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(71) Applicant (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): GRAHAM, Samuel, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HEIMBROOK, David, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KOBLAN, Kenneth, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). OLIFF, Allen, I. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). STIRDIVANT, Steven, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: A METHOD OF TREATING CANCER

(57) Abstract

The instant invention provides for a method of treating cancer which comprises administering to a mammal a composition which comprises a first compound which is an HMG-CoA reductase inhibitor and a second compound which is a farnesyl-protein transferase inhibitor.

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TITLE OF THE INVENTION
A METHOD OF TREATING CANCER

BACKGROUND OF THE INVENTION

The present invention relates to methods of treating cancer which comprise administering to a patient in need thereof a combination of an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) and an inhibitor of farnesyl-protein transferase.

Chemotherapy, the systematic administration of antineoplastic agents that travel throughout the body via the blood circulatory system, along with and often in conjunction with surgery and radiation treatment, has for years been widely utilized in the treatment of a wide variety of cancers. Unfortunately, the available chemotherapeutic drugs often fail patients because they kill many healthy cells and thus bring on serious side effects that limit the doses physicians can administer.

Prenylation of proteins by prenyl-protein transferases represents a class of post-translational modification (Glomset, J. A., Gelb, M. H., and Farnsworth, C. C. (1990), Trends Biochem. Sci. 15, 139-142; Maltese, W. A. (1990), FASEB J. 4, 3319-3328). This modification typically is required for the membrane localization and function of these proteins. Prenylated proteins share characteristic C-terminal sequences including CAAX (C, Cys; A, an aliphatic amino acid; X, another amino acid), XXCC, or XCXC. Three post-translational processing steps have been described for proteins having a C-terminal CAAX sequence: addition of either a 15 carbon (farnesyl) or 20 carbon (geranylgeranyl) isoprenoid to the Cys residue, proteolytic cleavage of the last 3 amino acids, and methylation of the new C-terminal carboxylate (Cox, A. D. and Der, C. J. (1992a), *Critical Rev. Oncogenesis* 3:365-400; Newman, C. M. H. and Magee, A. I. (1993), *Biochim. Biophys. Acta* 1155:79-96). Some proteins may also have a fourth modification: palmitoylation of one or two Cys residues

N-terminal to the farnesylated Cys. While some mammalian cell proteins terminating in XCXC are carboxymethylated, it is not clear whether carboxy methylation follows prenylation of proteins terminating with a XXCC motif (Clarke, S. (1992), Annu. Rev. Biochem. 61, 355-386). For all of the prenylated proteins, addition of the isoprenoid is the first step and is required for the subsequent steps (Cox, A. D. and Der, C. J. (1992a), *Critical Rev. Oncogenesis* 3:365-400; Cox, A. D. and Der, C. J. (1992b) *Current Opinion Cell Biol*. 4:1008-1016).

Three enzymes have been described that catalyze protein prenylation: farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). These enzymes are found in both yeast and mammalian cells (Clarke, 1992; Schafer, W. R. and Rine, J. (1992) *Annu. Rev. Genet*. 30:209-237). Each of these enzymes selectively uses farnesyl diphosphate or geranylgeranyl diphosphate as the isoprenoid donor and selectively recognizes the protein substrate. FPTase farnesylates CAAX-containing proteins that end with Ser, Met, Cys, Gln or Ala. For FPTase, CAAX tetrapeptides comprise the minimum region required for interaction of the protein substrate with the enzyme. The enzymological characterization of these three enzymes has demonstrated that it is possible to selectively inhibit one with little inhibitory effect on the others (Moores, S. L., Schaber, M. D., Mosser, S. D., Rands, E., O'Hara, M. B., Garsky, V. M., Marshall, M. S., Pompliano, D. L., and Gibbs, J. B., *J. Biol. Chem.*, 266:17438 (1991), U.S. Pat. No. 5,470,832).

The prenylation reactions have been shown genetically to be essential for the function of a variety of proteins (Clarke, 1992; Cox and Der, 1992a; Gibbs, J. B. (1991). *Cell* 65: 1-4; Newman and Magee, 1993; Schafer and Rine, 1992). This requirement often is demonstrated by mutating the CAAX Cys acceptors so that the proteins can no longer be prenylated. The resulting proteins are devoid of their central biological activity. These studies provide a genetic "proof of principle" indicating that inhibitors of prenylation can alter the physiological responses regulated by prenylated proteins.

The Ras protein is part of a signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation, Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Activation of Ras leads to activation of multiple intracellular signal transduction pathways, including the MAP Kinase pathway and the Rho/Rac pathway (Joneson *et al.*, Science *271*:810-812).

Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

The Ras protein is one of several proteins that are known to undergo post-translational modification. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al., J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)).

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa-Aaa-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence

for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)).

Other farnesylated proteins include the Ras-related GTP-binding proteins such as RhoB, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first class includes analogs of farnesyl diphosphate (FPP), while the second is related to protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al., ibid*; Reiss *et. al., ibid*; Reiss *et al., PNAS, 88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al., Science, 260*:1934-1937 (1993); Graham, et al., *J. Med. Chem., 37*, 725 (1994)).

Mammalian cells express four types of Ras proteins (H-, N-, K4A-, and K4B-Ras) among which K4B-Ras is the most frequently mutated form of Ras in human cancers. The genes that encode these proteins are abbreviated H-*ras*, N-*ras* , K4A-*ras* and K4B-*ras* respectively. H-*ras* is an abbreviation for Harvey-ras. K4A-*ras* and K4B-*ras* are abbreviations for the Kirsten splice variants of *ras* that contain the 4A and 4B exons, respectively. Inhibition of farnesyl-protein transferase has been shown to block the growth of H-*ras*-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the H-Ras

oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of H-*ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, *91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in H-*ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, inhibition of cell growth *in vitro* by lovastatin is not specific to cells transformed by mutated Ras proteins (DeClue, J.E. *et al.*, *Cancer Research*, 51:712-717 (1991)). It has also been observed that concentrations of lovastatin which inhibit 50% of sterol biosynthesis *in vitro* show no inhibitory activity against protein prenylation (Sinensky, M. *et al. J. Biol. Chem.*265:19937 (1990)).

It has been disclosed that the lysine-rich region and terminal CVIM sequence of the C-terminus of K4B-Ras confer resistance to inhibition of the cellular processing of that protein by certain selective FPTase inhibitors. (James, et al., *J. Biol. Chem. 270*, 6221 (1995)) Those FPTase inhibitors were effective in inhibiting the processing of H-Ras proteins. James et al., suggested that prenylation of the K4B-Ras protein by GGTase contributed to the resistance to the selective FPTase inhibitors. (Zhang et al, *J. Biol. Chem. 272* :10232-239 (1997); Rowell et al, *J. Biol. Chem. 272* :14093-14097 (1997); Whyte et al, *J. Biol. Chem. 272* :14459-14464 (1997)).

Several groups of scientists have recently disclosed compounds that inhibit both FPTase and GGTase (Lerner, et al., J. Biol. Chem. 270, 26770 (1995); and Graham, et al., J. Med. Chem. 37, 725 (1994)).

It has been disclosed that d-limonene and its metabolites may be used in combination with an HMG-CoA reductase inhibitor in the treatment of cancer (Japanese Pat. Publ. 07-316076). d-Limonene is described as an inhibitor of protein-farnesyl transferase in JP 07-316076, but the same group of scientists contemporaneously states that it has not been directly demonstrated that the compound is an inhibitor of farnesyl-protein transferase (*British J. Cancer*, 69:1015-1020 (1994)). There have been numerous scientific publications which describe d-limonene as a "weak inhibitor" of farnesyl-protein transferase (eg., M. H. Gelb et al. *Cancer Letters* 91:169-175 (1991); K. R. Stayrook et al. *Anticancer Research* 18:823-828 (1998)).

Pharmaceutical compositions that comprise compounds which are dual inhibitors of squalene synthetase and protein farnesyl-transferase and compounds which are HMG-CoA reductase inhibitor have been generally described (PCT Publs. WO 96/33159 and WO 96/34850).

It is the object of the present invention to provide a therapeutic composition which is useful in the treatment of cancer, and which may be characterized by efficacy *in vivo* as an inhibitor of the growth of cancer cells characterized by a mutated K4B-Ras protein, that comprises a first compound which is an HMG-CoA reductase inhibitor and a second compound which is an inhibitor of farnesyl-protein transferase.

It is also the object of the instant invention to provide a method of treating cancer which utilizes such a composition.

SUMMARY OF THE INVENTION

A method of treating cancer is disclosed which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a therapeutic composition that comprises a first compound which is an HMG-CoA reductase inhibitor, and a second compound which is an inhibitor of farnesyl-protein transferase.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: *Western Analysis SDS-PAGE Electrophoresis of PSN-1 cell lysates:*

The figure shows an X-ray film that was exposed to a PVDF membrane following transfer from a SDS-PAGE electrophoresis gel. The Western blot was developed with Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The proteins were isolated from the lysates of PSN-1 cells that had been exposed to vehicle (lane 1), 3 μM Compound 2 (Example 12) in the presence or absence of simvastatin as shown (lanes 2-4), 3 μM Compound 1 (Example 2) in the presence or absence of simvastatin as shown (lanes 5-7) and 3 μM Compound 3 (Example 16A) in the presence or absence of simvastatin as shown (lanes 8-10). Details of the assay procedure can be found in Example 24.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating cancer which is comprised of administering to a mammalian patient in need of such treatment an effective amount of a therapeutic composition that comprises a first compound which is an HMG-CoA reductase inhibitor, and a second compound which is an inhibitor of farnesyl-protein transferase. The present method of treating cancer by simultaneously inhibiting an enzyme which catalyzes the farnesylation of the cysteine residue of the CAAX motif and inhibiting production of polyisoprenoids including geranylgeranyl pyrophosphate offers advantages over previously disclosed methods which utilize a farnesyl-protein transferase inhibitor alone, in that the dosage of the inhibitor of farnesyl-protein transferase can be reduced. Any compounds which act as an HMG-CoA reductase inhibitor and any compounds which inhibit farnesyl-protein transferase can be used in the instant method. It is preferred that the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase.

When practicing the present method the HMG-CoA reductase inhibitor and the inhibitor of farnesyl-protein transferase may be administered either sequentially in any order or simultaneously.

However, it has been found that administration of the HMG-CoA reductase inhibitor from one to several days prior to administration of the inhibitor of farnesyl -protein transferase may be advantageous.

It is anticipated that the therapeutic effect of the instant compositions may be achieved with smaller amounts of the farnesyl-protein transferase inhibitor than would be required if such a farnesyl-protein transferase inhibitor was administered alone, thereby avoiding adverse toxicity effects which might result from administration of an amount of the farnesyl-protein transferase inhibitor sufficient to achieve the same therapeutic effect. It is further anticipated that the therapeutic effect of the instant compositions may be achieved with amounts of an inhibitor of HMG-CoA reductase that are known to be tolerated in man (see Thibault, A., Proc. Am. Assoc. Cancer Res., Vol. 35, Abstract 1351 (1994)). It is also anticipated that the instant compositions will achieve a synergistic therapeutic effect or will exhibit unexpected therapeutic advantage over the effect of any of the component compounds if administered alone.

The term prenyl-protein transferase inhibiting compound refers to compounds which antagonize, inhibit or counteract the expression of the gene coding a prenyl-protein transferase or the activity of the protein product thereof.

The terms farnesyl protein transferase inhibitor and inhibitor of farnesyl-protein transferase likewise refers to compounds which antagonize, inhibit or counteract the expression of the gene coding farnesyl-protein transferase or the activity of the protein product thereof.

The term selective as used herein refers to the inhibitory activity of the particular compound against farnesyl-protein transferase activity. The extent of selectivity of the farnesyl-protein transferase inhibitor component of the composition of the instant invention may affect the advantages that the method of treatment claimed herein offers over previously disclosed methods of using a combination of an HMG-CoA reductase inhibitor and compounds which are described as inhibitor of farnesyl-protein transferase. In particular, use of two

independent pharmaceutically active components that have complementary, essentially non-overlapping activities allows the person utilizing the instant method of treatment to independently and accurately vary the inhibitory activity of the combination without having to synthesize a single drug having a particular pharmaceutical activity profile. Preferably, for example, a selective inhibitor of farnesyl-protein transferase exhibits at least 20 times greater activity against farnesyl-protein transferase when comparing its activity against another receptor or enzymatic activity (such as geranylgeranyl-protein transferase type I or squalene synthetase), respectively. More preferably the selectivity is at least 100 times or more.

It is further preferred that the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase and is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 500 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

It is more preferred that the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase and is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 100 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

It is also preferred that the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase and is further characterized by:

b) an IC_{50} (a measure of in vitro inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than about 100-fold higher than the IC_{50} for the inhibition of the farnesylation of hDJ protein.

When measuring such IC_{50}s the assays described in Examples 23 and 24 may be utilized.

It is also preferred that the selective inhibitor of farnesyl-protein transferase is further characterized by:

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibition of K4B-Ras dependent activation of MAP kinases in cells at least 100-fold greater than the IC_{50} for inhibition of the farnesylation of the protein hDJ in cells.

It is also preferred that the selective inhibitor of farnesyl-protein transferase is further characterized by:

d) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells at least 1000 fold lower than the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

When measuring Ras dependent activation of MAP kinases in cells the assays described in Example 22 may be utilized.

It is preferred that the therapeutic compositions which are efficacious *in vivo* as an inhibitor of the growth of cancer cells characterized by a mutated K4B-Ras protein utilized in the instant invention are efficacious *in vivo* in the inhibition of both farnesylation and geranylgeranylation of the K4B-Ras protein. Preferably, such a composition, which may be termed a Class II prenyl-protein transferase inhibiting therapeutic composition, is characterized by the following *in vitro* activity in the assays described in the Examples (Criteria A):

a) inhibition of the cellular prenylation of greater than (>) about 50% of the newly synthesized K4B-Ras protein after incubation of assay cells with the composition of the invention.

Examples of assay cells that may be utilized to determine inhibition of cellular processing of newly synthesized protein that is a substrate of an enzyme that can modify the K4B-Ras protein C-terminus include 3T3, C33a, PSN-1 (a human pancreatic carcinoma cell line) and K-*ras*-transformed Rat-1 cells. Preferred assay cell lines have been found to be PSN-1. The preferred newly synthesized protein, whose percentage of processing is assessed in this assay, is selected from K4B-Ras and Rap1.

It is preferred that the concentration of the instant composition that is tested when evaluating whether the instant

therapeutic composition is characterized by Criteria A is a concentration that includes a concentration of less than (<) 5 μM of the farnesyl-protein transferase inhibitor and a concentration of < 1 μM of the HMG-CoA reductase inhibitor.

Methods for measuring the activity of the therapeutic composition utilized in the instant methods against the cellular processing of newly synthesized protein that is a substrate of an enzyme that can modify the K4B-Ras protein C-terminus after incubation of assay cells with the composition of the instant invention are described in Examples 23 and 24.

A Class II prenyl-protein transferase inhibiting therapeutic composition may also be characterized by (Criteria B):

b) inhibition of greater than (>) about 50% of the K4B-Ras dependent activation of MAP kinases in cells.

It is preferred that the concentration of the instant composition that is tested when evaluating whether the instant therapeutic composition is characterized by Criteria B is a concentration that includes a concentration of < 5 μM of the farnesyl-protein transferase inhibitor and a concentration of < 1 μM of the HMG-CoA reductase inhibitor. More preferably, the concentration of the instant composition that is tested for evaluating Criteria B is a concentration that includes a concentration of < 5 μM of the farnesyl-protein transferase inhibitor and a concentration of < 100 nM of the HMG-CoA reductase inhibitor.

A Class II prenyl-protein transferase inhibiting therapeutic composition may also be characterized by (Criteria C):

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibition of H-Ras dependent activation of MAP kinases in cells at least about 2 fold lower but less than about 20,000 fold lower than the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

It is preferred that the concentration of the instant composition that is tested when evaluating whether the instant therapeutic composition is characterized by Criteria C is a concentration that includes a concentration of < 5 μM of the farnesyl-protein transferase inhibitor and at a concentration of < 1 μM of the HMG-CoA

reductase inhibitor. More preferably, the concentration of the instant composition that is tested for evaluating Criteria C is a concentration that includes a concentration of < 5 μM of the farnesyl-protein transferase inhibitor and at a concentration of < 100 nM of the HMG-CoA reductase inhibitor.

Examples of assay cells that may be utilized to determine inhibition of Ras dependent activation of MAP kinases in cells include 3T3, C33a, PSN-1 (a human pancreatic carcinoma cell line) and K-*ras*-transformed Rat-1 cells. Preferred assay cell lines have been found to be C33a cells.

A method for measuring the activity of the therapeutic composition utilized in the instant methods against Ras dependent activation of MAP kinases in cells is described in Example 22.

It has been surprisingly found that combining a first compound that is an HMG-CoA reductase inhibitor and a second compound which is an inhibitor of farnesyl protein transferase, which is not characterized by any of the Criteria A, B and C hereinabove when it is tested in the absence of an HMG-CoA reductase inhibitor, will form a composition which is characterized by one or more of the Criteria A, B or C herein above. Such a therapeutic effect is also observed when the HMG-CoA reductase inhibitor is administered prior to the administration of the farnesyl-protein transferase inhibitor.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of this invention is greater than the sum of the effects that result from methods and compositions comprising the prenyl-protein transferase inhibitor and HMG-CoA reductase inhibitor of this invention separately and in the amounts employed in the methods and compositions hereof. Such synergy between the two active ingredients enabling smaller doses to be given and preventing or delaying the build up of multi-drug resistance.

The preferred therapeutic effect provided by the instant composition is the treatment of cancer and specifically the inhibition of cancerous tumor growth and/or the regression of cancerous tumors. Cancers which are treatable in accordance with the invention described herein include cancers of the brain, breast, colon, genitourinary tract,

prostate, skin, lymphatic system, pancreas, rectum, stomach, larynx, liver and lung. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, small cell lung cancers, bladder cancers, head and neck cancers, acute and chronic leukemias, melanomas, and neurological tumors.

The composition of this invention is also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the *ras* gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the instant composition to a mammal in need of such treatment. For example, the composition is useful in the treatment of neurofibromatosis, which is a benign proliferative disorder.

The composition of the instant invention is also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant composition may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al. *American Journal of Pathology*, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The instant composition may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant composition may also be useful in the treatment of certain forms of vision deficit related to retinal vascularization.

The instant composition may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The instant composition may also be useful in the inhibition of proliferation of vascular smooth muscle cells and therefore useful in the prevention and therapy of arteriosclerosis and diabetic vascular pathologies.

The instant composition may comprise a combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, according to standard pharmaceutical practice. The composition may be administered to mammals, preferably humans. The instant composition can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredients may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending

agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating

concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The instant compositions may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compositions of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery

system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

The combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor of the instant method may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant combination may be useful in further combination with known anti-cancer and cytotoxic agents. Similarly, the instant combination may be useful in further combination with agents that are effective in the treatment and prevention of neurofibromatosis, restinosis, polycystic kidney disease, infections of hepatitis delta and related viruses and fungal infections. The instant combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation.

The instant combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor may be utilized in combination with farnesyl pyrophosphate competitive inhibitors of the activity of farnesyl-protein transferase or in combination with a compound which has Raf antagonist activity. The instant combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor may also be co-administered with compounds that are selective inhibitors of geranylgeranyl protein transferase or dual inhibitors of farnesyl-protein transferase and geranylgeranyl-protein transferase.

The composition of the instant invention may also be co-administered with other well known cancer therapeutic agents that are selected for their particular usefulness against the condition that is being treated. Included in such combinations of therapeutic

agents are combinations of the instant farnesyl-protein transferase inhibitors and an antineoplastic agent. It is also understood that the instant combination of a combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor may be used in conjunction with other methods of treating cancer and/or tumors, including radiation therapy and surgery.

If formulated as a fixed dose, such combination products employ the combinations of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Combinations of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a multiple combination formulation is inappropriate.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with a combination of an inhibitor of farnesyl-protein transferase and an HMG-CoA reductase inhibitor.

Additionally, compositions of the instant invention may also be useful as radiation sensitizers, as described in WO 97/38697, published on October 23, 1997, and herein incorporated by reference. In particular, the composition of the instant invention may be administered to a patient in need prior to the application of radiation therapy. In another embodiment of the instant method of treatment, an HMG-CoA reductase inhibitor is administered prior to the administration of an inhibitor of farnesyl-protein transferase, and administration of radiation therapy is either at the same time as administration of the inhibitor of farnesyl-protein transferase or after the administration of the inhibitor of farnesyl-protein transferase.

The instant composition may also be useful in combination with an integrin antagonist for the treatment of cancer, as described in U.S. Ser. No. 09/055,487, filed April 6, 1998, which is incorporated herein by reference.

As used herein the term an integrin antagonist refers

to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to an integrin(s) that is involved in the regulation of angiogenisis, or in the growth and invasiveness of tumor cells. In particular, the term refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 3$ integrin, which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin, or which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The term also refers to antagonists of any combination of $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$ integrins. The instant compounds may also be useful with other agents that inhibit angiogenisis and thereby inhibit the growth and invasiveness of tumor cells, including, but not limited to angiostatin and endostatin.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of a farnesyl-protein transferase inhibitor and a suitable amount of an HMG-CoA reductase inhibitor are administered to a mammal undergoing treatment for cancer. Administration occurs in an amount of each type of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. A particular daily therapeutic dosage that comprises the instant composition includes from about 10 mg to about 3000mg of a farnesyl-protein transferase inhibitor and about 0.1mg to about 3000mg of an HMG-CoA reductase inhibitor. Preferably, the daily dosage comprises from about 10mg to about 1000mg of a farnesyl-protein transferase inhibitor and about 0.3mg to about 160mg of an HMG-CoA reductase inhibitor.

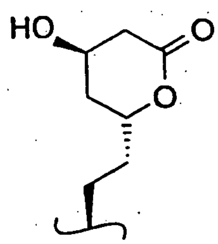
Examples of an antineoplastic agent include, in general, microtubule-stabilising agents (such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), or their derivatives); alkylating agents, anti-metabolites; epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes; biological response modifiers and growth inhibitors; hormonal/anti-hormonal therapeutic agents and haematopoietic growth factors.

Example classes of antineoplastic agents include, for example, the anthracycline family of drugs, the vinca drugs, the mitomycins, the bleomycins, the cytotoxic nucleosides, the taxanes, the epothilones, discodermolide, the pteridine family of drugs, diynenes and the podophyllotoxins. Particularly useful members of those classes include, for example, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, dichloro-methotrexate, mitomycin C, porfiromycin, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podo-phyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine, leurosine, paclitaxel and the like. Other useful antineoplastic agents include estramustine, cisplatin, carboplatin, cyclophosphamide, bleomycin, gemcitibine, ifosamide, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, CPT-11, topotecan, ara-C, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons and interleukins.

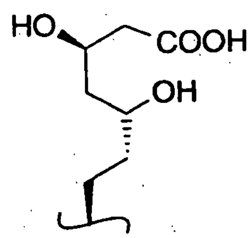
A compound which inhibits HMG-CoA reductase is used to practice the instant invention. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see US

Patent No. 4,231,938; 4,294,926; 4,319,039), simvastatin (ZOCOR®; see US Patent No. 4,444,784; 4,820,850; 4,916,239), pravastatin (PRAVACHOL®; see US Patent Nos. 4,346,227; 4,537,859; 4,410,629; 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see US Patent Nos. 5,354,772; 4,911,165; 4,929,437; 5,189,164; 5,118,853; 5,290,946; 5,356,896), atorvastatin (LIPITOR®; see US Patent Nos. 5,273,995; 4,681,893; 5,489,691; 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone
I



Open-Acid
II

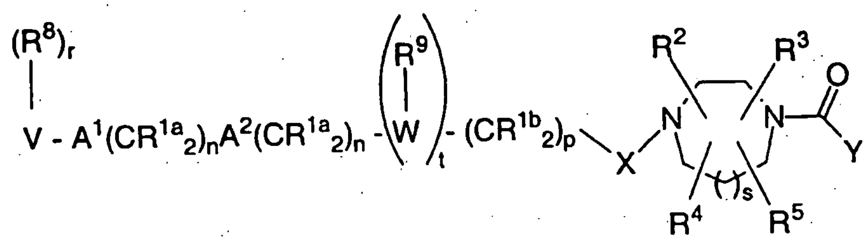
In HMG-CoA reductase inhibitor's where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term “HMG-CoA reductase inhibitor” as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically

acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl)aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

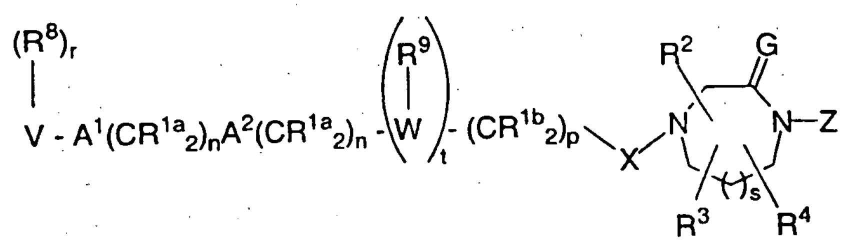
Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

Examples of farnesyl-protein transferase inhibiting compounds include the following:

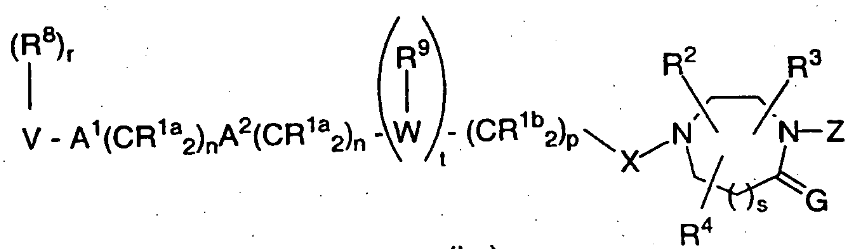
(a) a compound represented by formula (I-a) through (I-c):



(I-a)

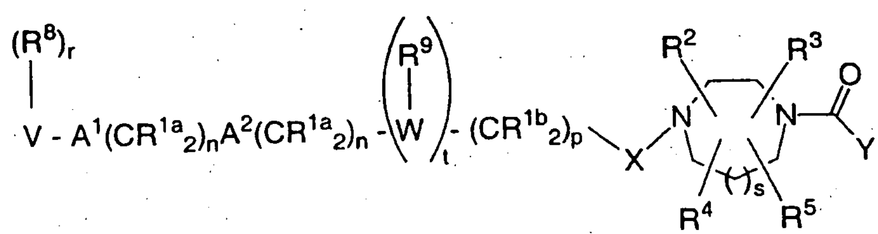


(I-b)



(I-c)

wherein with respect to formula (I-a):



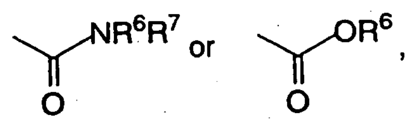
(I-a)

or a pharmaceutically acceptable salt thereof,

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclyl, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)$-NR^{10}-;

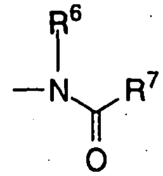
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

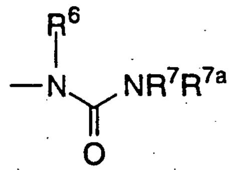


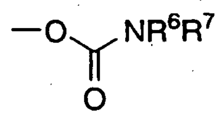
wherein the substituted group is substituted with one or more of:

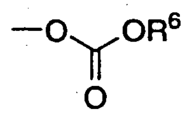
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^6, $S(O)R^6$, SO_2R^6,

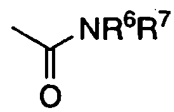
5) $-NR^6R^7$,

6)  ,

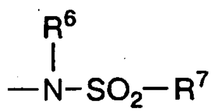
7)  ,

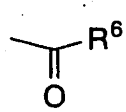
8)  ,

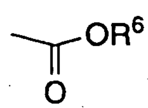
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

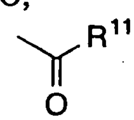
12)  ,

13)  , or

14)  ; or

R^2 and R^3 are attached to the same C atom and are combined to form - $(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

R^4 and R^5 are independently selected from H and CH_3; and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom; R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $R^{10}{}_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, CN, H_2N-$C(NH)$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

W is a heterocycle;

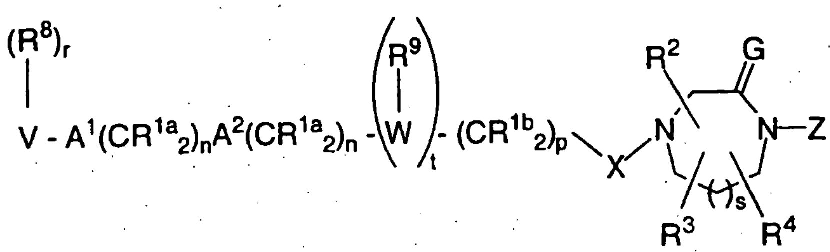
X is -CH_2-, -C(=O)-, or -S(=O)$_m$-;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen;
s is	0 or 1;
t is	0 or 1; and
u is	4 or 5;

with respect to formula (I-b):



(I-b)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, R^{7a}, u, R^8, A^1, A^2, V, W, X, n, p, r, s, t and u are as defined above with respect to formula (I-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-C-(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

G is H_2 or O;

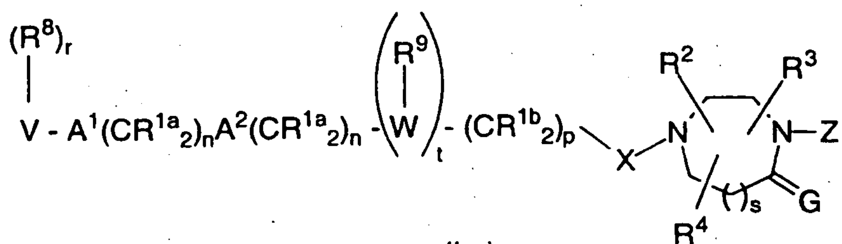
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) aryl or heterocycle,
e) HO,
f) $-S(O)_mR^6$, or
g) $-C(O)NR^6R^7$;

2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

with respect to formula (I-c):



(I-c)

or a pharmaceutically acceptable salt thereof,

R^{1a}, R^{1b}, R^{10}, R^{11}, m, R^2, R^3, R^6, R^7, p, u, R^{7a}, R^8, A^1, A^2, V, W, X, n, r and t are as defined above with respect to formula (I-a);

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

G is O;

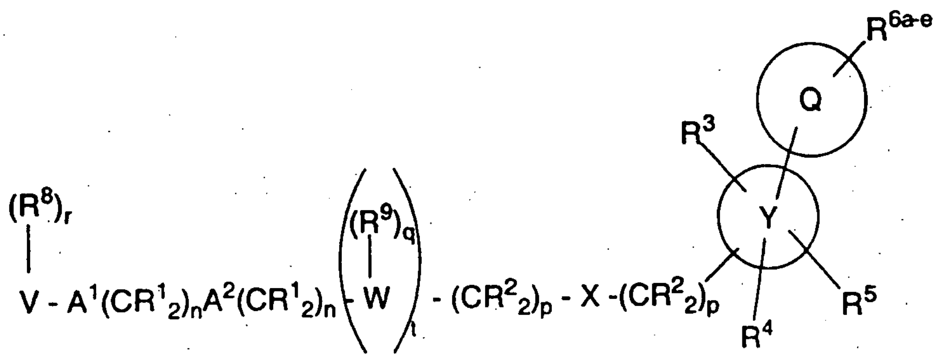
Z is aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^6$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^6$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

and

s is 1;

(b) a compound represented by formula (II):



II

wherein:

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y;

Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

R^1 and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $R^{11}C(O)O$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic,

C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^3, R^4 and R^5 are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{11}C(O)O$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted C_1-C_6 alkyl,

d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic,

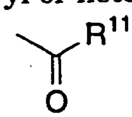
C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^7 is selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c)  ,

d) $-SO_2R^{11}$,

e) $N(R^{10})_2$ or

f) C_{1-4} perfluoroalkyl;

R^8 is independently selected from:

a) hydrogen,

b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{11}S(O)_2NR^{10}$-, $(R^{10})_2NS(O)_2$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3,

$-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is independently selected from:

a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterary l, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

R^{13} is selected from hydrogen, C_1-C_6 alkyl, cyano, C_1-C_6 alkylsulfonyl and C_1-C_6 acyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^{10}$-, $-NR^{10}C(O)$-, O, $-N(R^{10})$-, $-S(O)_2N(R^{10})$-, $-N(R^{10})S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

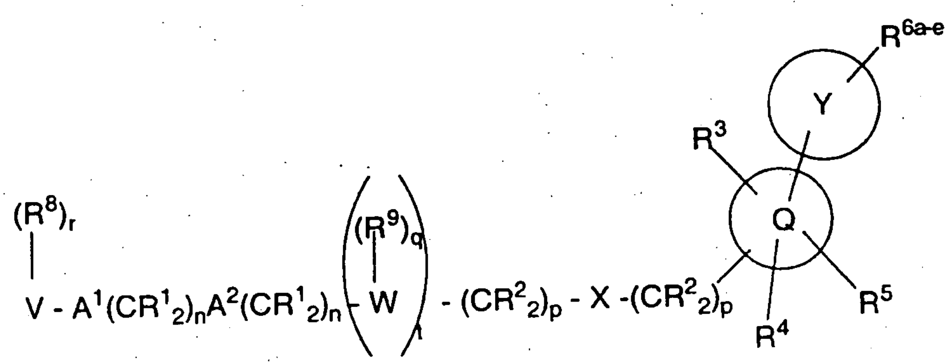
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is a bond, -CH=CH-, O, -C(=O)-, -C(O)NR^7-, -NR^7C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^7C(O)-, -NR^7-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$- or -$S(=O)_m$-;

m is 0, 1 or 2;
n is independently 0, 1, 2, 3 or 4;
p is independently 0, 1, 2, 3 or 4;
q is 0, 1, 2 or 3;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 0 or 1;

(c) a compound represented by formula (III):

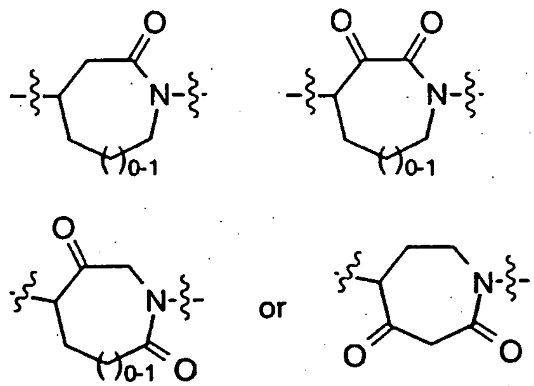


III

wherein:

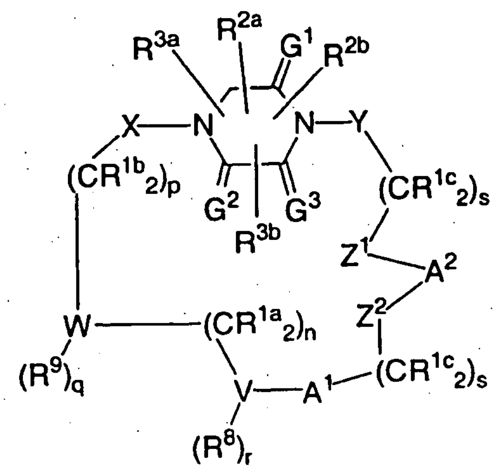
R^1, R^2, R^3, R^4, R^5, R^{6a-e}, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, A^1, A^2, V, W, m, n, p, q, r and t are as previously defined with respect to formula (II);

Q is a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, $-C(=NR^{13})-$ or sulfonyl moiety adjacent to the nitrogen atom attached to Y, provided that Q is not



Y is a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom;

(d) a compound represented by formula (IV):



IV

wherein:

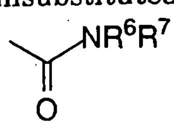
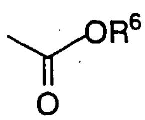
R^{1a}, R^{1b}, R^{1c} and R^{1d} are independently selected from:

a) hydrogen,

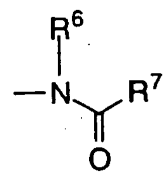
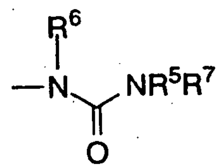
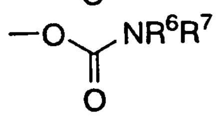
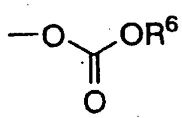
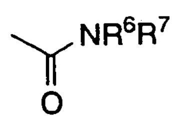
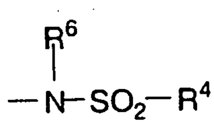
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

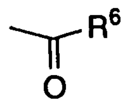
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

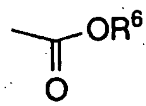
R^{2a}, R^{2b}, R^{3a} and R^{3b} are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

 or ,

wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) $C_{1\text{-}4}$ alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
2) $C_{3\text{-}6}$ cycloalkyl,
3) OR^6,
4) SR^4, $S(O)R^4$, SO_2R^4,
5) $—NR^6R^7$,
6)  ,
7)  ,
8)  ,
9)  ,
10)  ,
11) $—SO_2—NR^6R^7$,
12)  ,

13)  ,

14)  ,

15) N_3, or

16) F; or

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

and R^2 and R^3 are optionally attached to the same carbon atom;

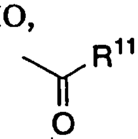
R^4 is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$;

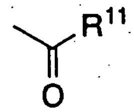
R^5, R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e)  ,

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring; and independently, R^5 and R^7 may be joined in a ring;

R^8 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, unsubstituted or substituted aryl and unsubstituted or substituted heterocycle;

R^{11} is independently selected from C_1-C_6 alkyl unsubstituted or substituted aryl and unsubstituted or substituted heterocycle;

A^1 is selected from: a bond, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, and $S(O)_m$;

A^2 is selected from: a bond, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, $S(O)_m$ and -$C(R^{1d})_2$-;

G^1, G^2 and G^3 are independently selected from: H_2 and O;

W is heterocycle;

V is selected from:

a) heterocycle, and

b) aryl;

X and Y are independently selected from: a bond, -C(=O)- or -$S(=O)_m$-;

Z^1 is selected from: unsubstituted or substituted aryl and unsubstituted or substituted heterocycle, wherein the substituted aryl or substituted heterocycle is substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^4$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^4$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

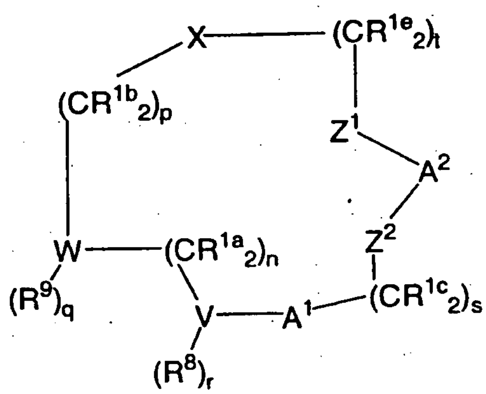
Z^2 is selected from: a bond, unsubstituted or substituted aryl and unsubstituted or substituted heterocycle, wherein the substituted aryl or substituted heterocycle is substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^4$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,

5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^4$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5;
s is independently 0, 1, 2 or 3; and
u is 4 or 5;

(f) a compound represented by formula (V):



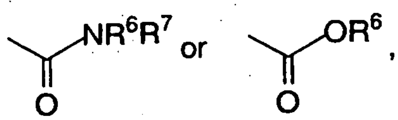
V

wherein:
R^{1a}, R^{1b}, R^{1c}, R^{1d} and R^{1e} are independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-,

$(R^{10})_2N-C(O)-$, CN, NO_2, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, CN, $(R^{10})_2N-C(NR^{10})-$, $R^{10}C(O)-$, $R^{10}OC(O)-$, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)-NR^{10}-$;

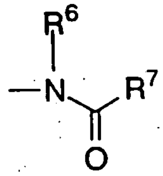
R^{2a}, R^{2b}, R^{3a} and R^{3b} are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

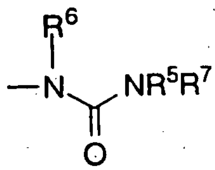


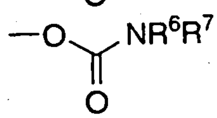
wherein the substituted group is substituted with one or more of:

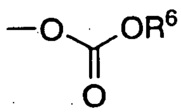
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^4, $S(O)R^4$, SO_2R^4,

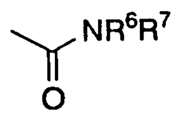
5) $-NR^6R^7$,

6)  ,

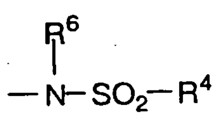
7)  ,

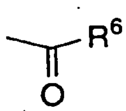
8)  ,

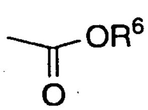
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

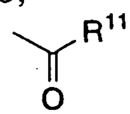
15) N_3, or

16) F; or

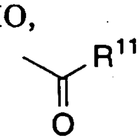
R^2 and R^3 are attached to the same C atom and are combined to form - $(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -N(COR^{10})- ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^4 is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $—SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^5, R^6 and R^7 are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $—SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring; and independently,

R^5 and R^7 may be joined in a ring;

R^8 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, unsubstituted or substituted aryl and unsubstituted or substituted heterocycle;

R^{11} is independently selected from C_1-C_6 alkyl unsubstituted or substituted aryl and unsubstituted or substituted heterocycle;

A^1 is selected from: a bond, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, and S(O)$_m$;

A^2 is selected from: a bond, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, S(O)$_m$ and -C(R^{1d})$_2$-;

W is heteroaryl;

V is selected from:

a) heteroaryl, and
b) aryl;

X is selected from: -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}C(O)-O-, -O-C(O)NR^{10}-, - NR^{10}C(O)NR^{10}-, - C(O)NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$- and S(O)$_m$;

Z^1 is selected from: unsubstituted or substituted aryl and unsubstituted or substituted heteroaryl, wherein the substituted aryl or substituted heteroaryl is substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
 a) C_{1-4} alkoxy,
 b) NR^{6}R^7,
 c) C_{3-6} cycloalkyl,
 d) aryl or heterocycle,
 e) HO,
 f) -S(O)$_m$R^4, or
 g) -C(O)NR^{6}R^7,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^{6}R^7,
6) CN,

7) NO_2,
8) CF_3;
9) $-S(O)_mR^4$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

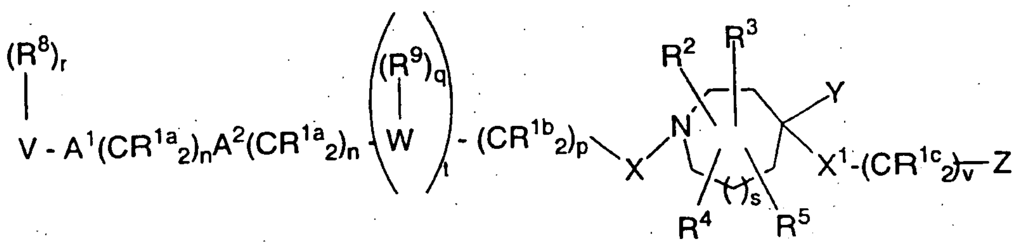
Z^2 is selected from: a bond, unsubstituted or substituted aryl and unsubstituted or substituted heteroaryl, wherein the substituted aryl or substituted heteroaryl is substituted with one or more of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^4$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^4$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;

r is 0 to 5;
s is independently 0, 1, 2 or 3;
t is 1, 2, 3 or 4; and
u is 4 or 5;

(g) a compound represented by formula (VI):



VI

wherein:
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

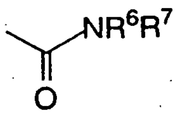
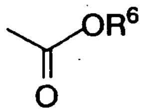
R^{1c} is selected from:

a) hydrogen,
b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-,

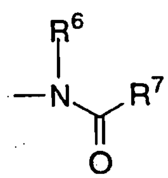
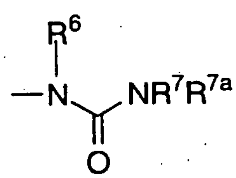
$R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

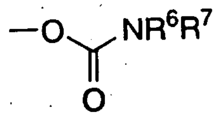
c) unsubstituted or substituted aryl;

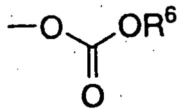
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, OR^{10},

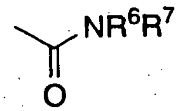
 or  ,

wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $—NR^6R^7$,
6)  ,
7)  ,

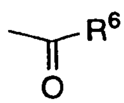
8)  ,

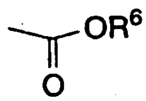
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12) $-N(R^6)-SO_2-R^{6a}$,

13)  ,

14)  ,

15) N_3,

16) F, or

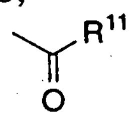
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 and R^5 are independently selected from H and CH_3;

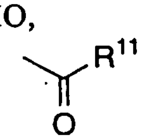
and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl or substituted heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle,

wherein the substituted alkyl, substituted aryl or substituted heterocycle is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

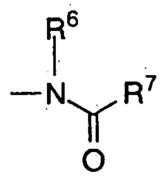
a) C_{1-4} alkyl,

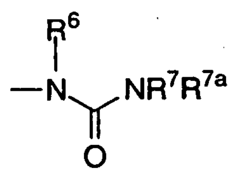
b) $(CH_2)_pOR^6$,

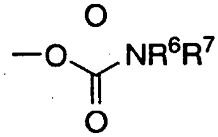
c) $(CH_2)_pNR^6R^7$,
d) halogen,
e) CN,
f) aryl or heteroaryl,
g) perfluoro-C_{1-4} alkyl,
h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

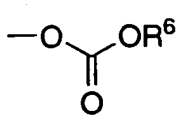
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

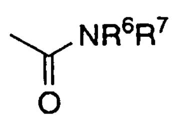
5) $—NR^6R^7$,

6)  ,

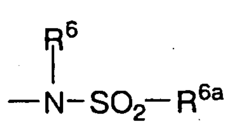
7)  ,

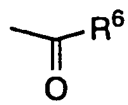
8)  ,

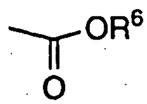
9)  ,

10)  ,

11) $—SO_2—NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F,

17) perfluoro-C_{1-4}-alkyl, or

18) C_{1-6}-alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

W is a heterocycle;

X is a bond, -CH_2-, -C(=O)-, -NR^6C(=O)- or -S(=O)$_m$-;

X^1 is a bond, -C(=O)-, -NR^6C(=O)-, -NR^6-, -O- or -S(=O)$_m$-;

Y is selected from:

a) hydrogen,

b) $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{12}C(O)$-, $R^{10}OC(O)$-, N_3, F, -N$(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, $R^{10}C(O)$- and $R^{10}OC(O)$-;

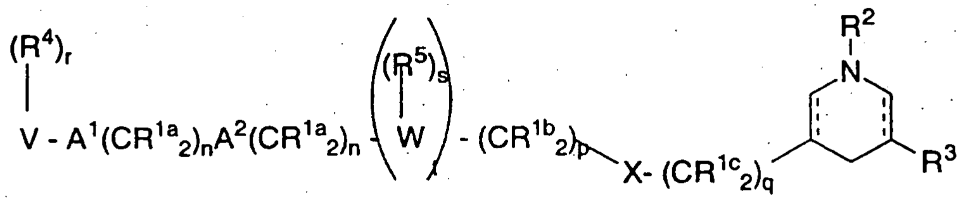
Z is an unsubstituted or substituted group selected from aryl and heterocycle, wherein the substituted group is substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -$S(O)_mR^{6a}$, or
   g) -C(O)NR^6R^7,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) -$S(O)_mR^{6a}$,
10) -C(O)NR^6R^7, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;

r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1;
u is 4 or 5; and
v is 0, 1 or 2;

(g) a compound represented by formula (VII):



VII

wherein:

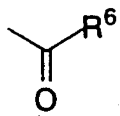
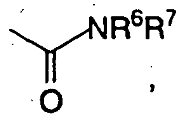
R^{1a}, R^{1b} and R^{1c} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)$-NR^8-;

R^2 is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,

, , and $-S(O)_2R^6$,

wherein the substituted group is substituted with one or more of:

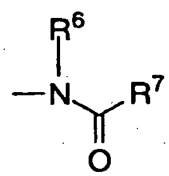
1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
   - a) C_{1-4} alkyl,
   - b) $(CH_2)_pOR^6$,
   - c) $(CH_2)_pNR^6R^7$,
   - d) halogen,
   - e) C_{1-4} perfluoroalkyl,

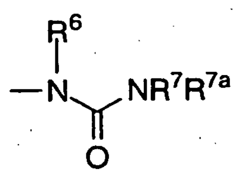
2) C_{3-6} cycloalkyl,

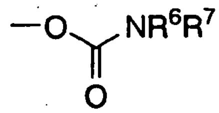
3) OR^6,

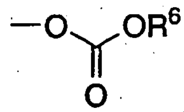
4) SR^6, $S(O)R^6$, SO_2R^6,

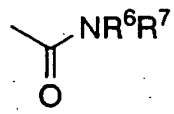
5) $—NR^6R^7$,

6)  ,

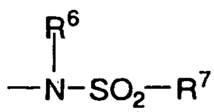
7)  ,

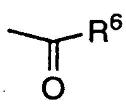
8)  ,

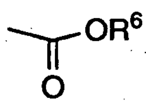
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

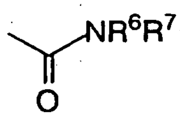
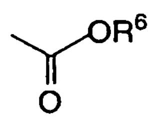
12)  ,

13)  ,

14)  ,

15) C_{1-8} alkyl, or

16) C_{1-8} perfluoroalkyl;

R^3 is selected from: H;  or  ,

R^4 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-C(NH)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-;

R^5 is independently selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

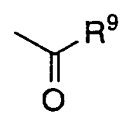
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, C_{1-4} perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

a) C_{1-4} alkoxy,

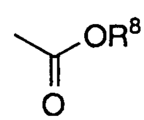
b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

c) halogen,

d) HO,

e) 

,

f) 

,

g) $-S(O)_mR^9$, or

h) $N(R^8)_2$; or

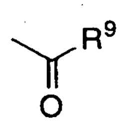
R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

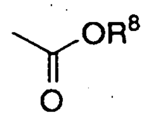
R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

R^{10} is selected from: H; $R^8C(O)$-; $R^9S(O)_m$-; unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

e)  ,

f)  ,

g) $-S(O)_mR^9$,

h) $N(R^8)_2$, or
i) C_{3-6} cycloalkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, $-NR^8C(O)$-, O, $-N(R^8)$-, $-S(O)_2N(R^8)$-,

$-N(R^8)S(O)_2-$, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

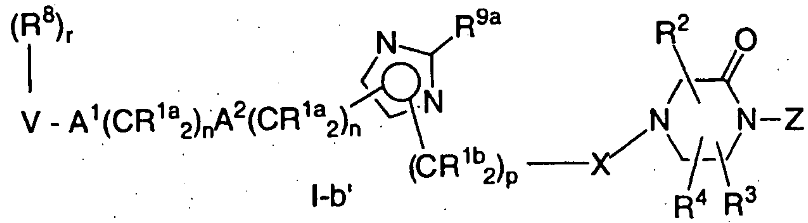
X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$, $-NR^{10}-$, O or $-C(=O)-$;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
q is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen;
s is	1 or 2;
t is	0 or 1; and

the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt or disulfide thereof.

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula I-b':



I-b'

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

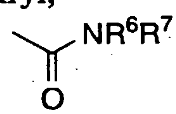
a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

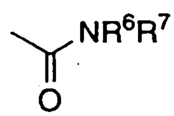
R^3 and R^4 selected from H and CH_3;

R^2 is selected fromH; unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



;

or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen,
c) perfluoro-C_{1-4} alkyl, or
d) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 perfluoroalkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is $-CH_2-$ or -C(=O)-;

Z is selected from:

1) a unsubstituted or substituted group selected from aryl, heteroaryl, arylmethyl, heteroarylmethyl, arylsulfonyl, heteroarylsulfonyl, wherein the substituted group is substituted with one or more of the following:

a) C_{1-4} alkyl, unsubstituted or substituted with: C_{1-4} alkoxy, NR^6R^7, C_{3-6} cycloalkyl, unsubstituted or substituted aryl, heterocycle, HO, $-S(O)_mR^{6a}$, or $-C(O)NR^6R^7$,

b) aryl or heterocycle,

c) halogen,

d) OR^6,

e) NR^6R^7,

f) CN,

g) NO_2,

h) CF_3;

i) $-S(O)_mR^{6a}$,

j) $-C(O)NR^6R^7$, or

k) C_3-C_6 cycloalkyl; or

2) unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,

wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

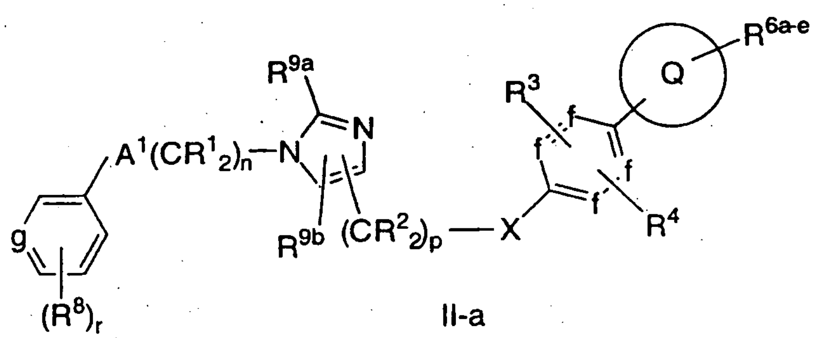
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen;

provided that the substituent $(R^8)_r$- V - $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ - is not H;

or a pharmaceutically acceptable salt thereof.

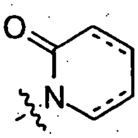
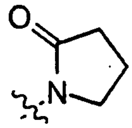
In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula II-a:



II-a

wherein:

Q is selected from

 and 

from 0-2 of f(s) are independently N, and the remaining f's are independently CH;

g is selected from N and CH;

R^1 is selected from: hydrogen, C_3-C_{10} cycloalkyl or C_1-C_6 alkyl;

R^2 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$, F or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

R^3 is selected from:
a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^4 is selected from H, halogen, C_1-C_6 alkyl and CF_3;

R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen, C_1-C_6 perfluoroalkyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,
c) unsubstituted C_1-C_6 alkyl,
d) substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{12}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-; or

any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH-, -CH=CH-CH_2-, -$(CH_2)_4$- and -$(CH_2)_3$-;

R^8 is independently selected from:

a) hydrogen,
b) aryl, substituted aryl, heterocycle, substituted heterocycle, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} and R^{9b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, amino-C_1-C_6 alkyl, N-(unsubstituted or substituted benzolyl)-amino-C_1-C_6 alkyl, (C_1-C_6 alkyl)$_2$-amino-C_1-C_6 alkyl, acetylamino-C_1-C_6 alkyl, phenyl-C_1-C_6 alkyl, 2,2,2-trifluoroethyl, aryl and substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 aralkyl, C_1-C_6 substituted aralkyl, C_1-C_6 heteroaralkyl, C_1-C_6 substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, substituted heterаryl, C_1-C_6 perfluoroalkyl, 2-aminoethyl and 2,2,2-trifluoroethyl;

A^1 is selected from: a bond, -C(O)-, O, -N(R^{10})-, or S(O)$_m$;

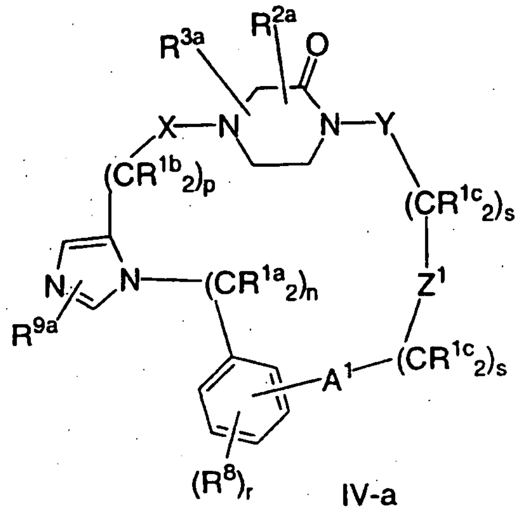
X is a bond, -CH=CH-, -C(O)NR^{10}-, -NR^{10}C(O)-, -NR^{10}-, O or -C(=O)-,

n is	0 or 1; provided that n is not 0 if A^1 is a bond, O, -N(R^{10})- or S(O)$_m$;
m is	0, 1 or 2;
p is	0, 1, 2, 3 or 4; and
r is	0, 1 or 2;

the dashed lines (- - -) represent optional double bonds;

or a pharmaceutically acceptable salt thereof.

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula IV-a:



IV-a

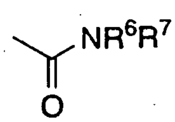
wherein:

R1a is selected from: hydrogen and C_1-C_6 alkyl;

R^{1b} and R^{1c} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

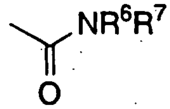
R^{3a} is selected from H and CH_3;
R^{2a} is selected from H;


;

and C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,

4) SR^{6a}, SO_2R^4, or

5)  ;

and any two of R^2 and R^3 are optionally attached to the same carbon atom;

R^4 is selected from:

C_{1-4} alkyl and C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^6 and R^7 are independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^8 is independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by unsubstituted or substituted aryl, C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and unsubstituted or substituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and unsubstituted or substituted aryl;

A^1 is selected from: a bond, -C(O)- and O;

X is a bond;

Y is a bond;

Z^1 is selected from:

unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted aryl or substituted heterocycle is substituted with one or two of:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^4$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^4$,
10) $-C(O)NR^6R^7$, or

11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5; and
s is independently 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Specific compounds which are inhibitors of farnesyl-protein transferase and are therefore useful in the present invention include:
5(S)-n-Butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

(S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl)-2-piperazinone

5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone

1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine

4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile (L-806,572)

4-{5-[4-Hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(5-Chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile

18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclononadecine-9-carbonitrile,

(±)-19,20-Dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile,

19,20-Dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile (**3**),

(±)-19,20-Dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile,

or the pharmaceutically acceptable salt thereof.

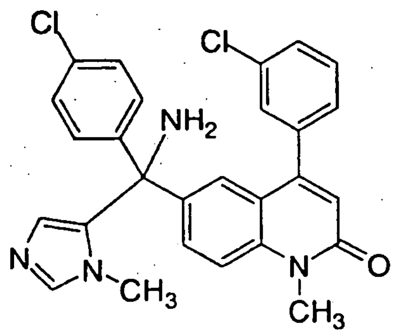
Inhibitors of farnesyl-protein transferase which are useful as a component in the instant composition, and methods of synthesis of such inhibitors, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

WO 96/30343 (October 3, 1996); USSN 08/412,829 filed on March 29, 1995; and USSN 08/470,690 filed on June 6, 1995; and USSN 08/600,728 filed on February 28, 1996;
WO 97/18813 (May 29, 1997); USSN 08/749,254 filed on November 15, 1996;
WO 97/38665 (October 23, 1997); USSN 08/831,308 filed on April 1, 1997;
WO 98/28980, (July 9, 1998); USSN 08/997,171 filed on December 22, 1997;
WO 98/29119, (July 9, 1998); USSN 08/995,744 filed on December 22, 1997; and
USSN 60/091,629, filed on July 2, 1998; and
USSN 60/091,513, filed on July 2, 1998.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

The following compounds which are inhibitors of farnesyl-protein transferase are particularly useful when combined with an

HMG-CoA reductase inhibitor in a composition that is useful in the treatment of cancer:
(±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound J)



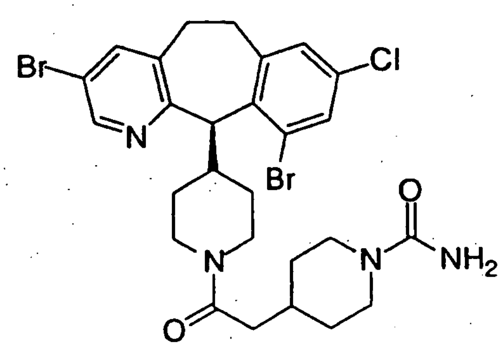
J

(-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound J-A; designated "comp. 74" in WO 97/21701)

(+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound J-B; designated "comp. 75" in WO 97/21701)

or a pharmaceutically acceptable salt thereof. The syntheses of these compounds are specifically described in PCT Publication WO 97/21701, in particular on pages 19-28. The preferred compound among these compounds to use in combination with an HMG-CoA reductase inhibitor is Compound J-B.

The following compound which is an inhibitor of farnesyl-protein transferase is particularly useful when combined with an HMG-CoA reductase inhibitor in a composition that is useful in the treatment of cancer:



or a pharmaceutically acceptable salt thereof. The synthesis of this compound is specifically described in PCT Publication WO 97/23478, in particular on pages 18-56. In WO 97/23478, the above compound is designated compound "39.0" and is specifically described in Example 10.

Compounds which are described as inhibitors of farnesyl-protein transferase and may therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference:

WO 95/32987 published on 7 December 1995;
U. S. Pat. No. 5,420,245;
U. S. Pat. No. 5,523,430;
U. S. Pat. No. 5,532,359;
U. S. Pat. No. 5,510,510;
U. S. Pat. No. 5,589,485;
U. S. Pat. No. 5,602,098;
European Pat. Publ. 0 618 221;
European Pat. Publ. 0 675 112;
European Pat. Publ. 0 604 181;
European Pat. Publ. 0 696 593;
WO 94/19357;
WO 95/08542 ;
WO 95/11917;
WO 95/12612;
WO 95/12572;
WO 95/10514 and U.S. Pat. No. 5,661,152;

WO 95/10515;
WO 95/10516;
WO 95/24612;
WO 95/34535;
WO 95/25086;
WO 96/05529;
WO 96/06138;
WO 96/06193;
WO 96/16443;
WO 96/21701;
WO 96/21456;
WO 96/22278;
WO 96/24611;
WO 96/24612;
WO 96/05168;
WO 96/05169;
WO 96/00736 and U.S. Pat. No. 5,571,792 granted on November 5, 1996;
WO 96/17861;
WO 96/33159;
WO 96/34850;
WO 96/34851;
WO 96/30017;
WO 96/30018;
WO 96/30362;
WO 96/30363;
WO 96/31111;
WO 96/31477;
WO 96/31478;
WO 96/31501;
WO 97/00252;
WO 97/03047;
WO 97/03050;
WO 97/04785;
WO 97/02920;
WO 97/17070;

WO 97/23478;
WO 97/26246;
WO 97/30053;
WO 97/44350;
WO 98/02436; and
U. S. Pat. No. 5,532,359 granted on July 2, 1996.

With respect to the compounds of formulae I through VII and I-a through IV-a the following definitions apply:

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

Heteroalkyl refers to an alkyl group having from 2-15 carbon atoms, and interrupted by from 1-4 heteroatoms selected from O, S and N.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, isoprenyl, farnesyl, geranyl, geranylgeranyl and the like. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups. With regard to the farnesyl transferase inhibitors, "aryl" is intended to include any stable monocyclic, bicyclic or tricyclic carbon ring(s) of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl groups include phenyl, naphthyl, anthracenyl, biphenyl, tetrahydronaphthyl, indanyl, phenanthrenyl and the like.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole,

oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine, pyrazine and triazine. Examples of partially aromatic groups are tetrahydro-imidazo[4,5-c]pyridine, phthalidyl and saccharinyl, as defined below.

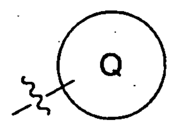
With regard to the farnesyl transferase inhibitors, the term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic or stable 11-15 membered tricyclic heterocycle ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydro-benzothienyl, dihydrobenzothiopyranyl, dihydrobenzothio-pyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyridyl N-oxide, pyridonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolinyl N-oxide, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from imidazolyl, 2-oxopyrrolidinyl, piperidyl, pyridyl and pyrrolidinyl.

With regard to the farnesyl transferase inhibitors, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, N(C_1-C_6 alkyl)$_2$, NO_2, CN, (C_1-C_6 alkyl)O-, -OH, (C_1-C_6 alkyl)S(O)$_m$-, (C_1-C_6 alkyl)C(O)NH-, H_2N-C(NH)-,

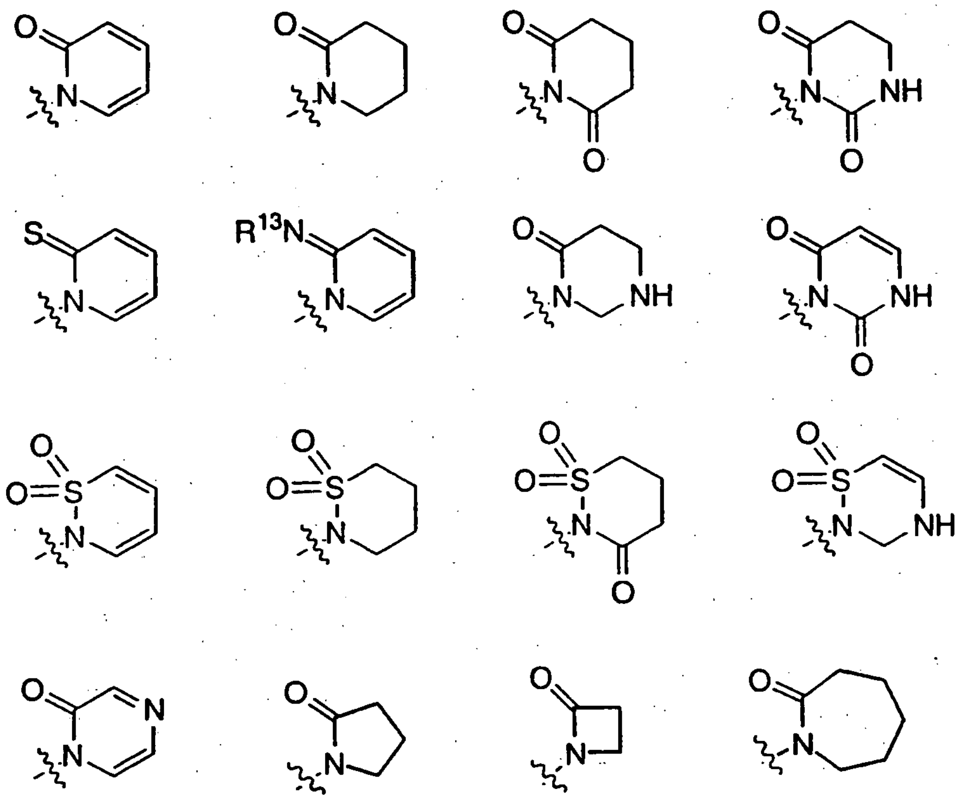
$(C_1\text{-}C_6$ alkyl)C(O)-, $(C_1\text{-}C_6$ alkyl)OC(O)-, N_3,$(C_1\text{-}C_6$ alkyl)OC(O)NH- and $C_1\text{-}C_{20}$ alkyl.

The compounds used in the present method may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. Unless otherwise specified, named amino acids are understood to have the natural "L" stereoconfiguration.

With respect to the farnesyl-protein transferase inhibitors of the formula II, the substituent illustrated by the structure:

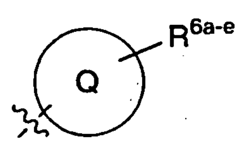


represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

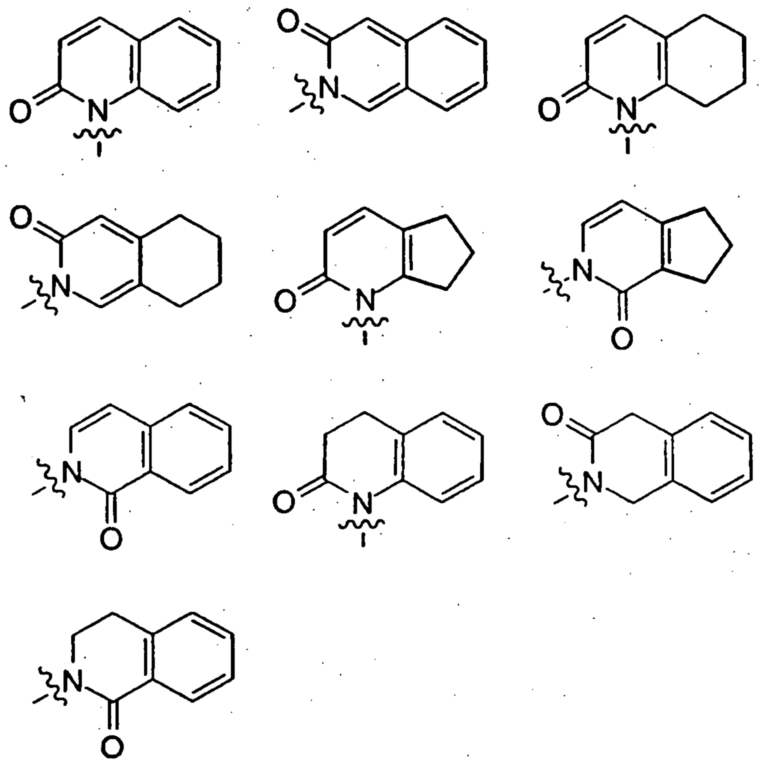


It is understood that such rings may be substituted by R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors of the formula II, the moiety described as

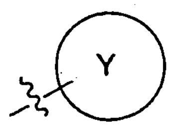


where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, -$(CH_2)_4$- and -$(CH_2)_4$- includes, but is not limited to, the following structures:

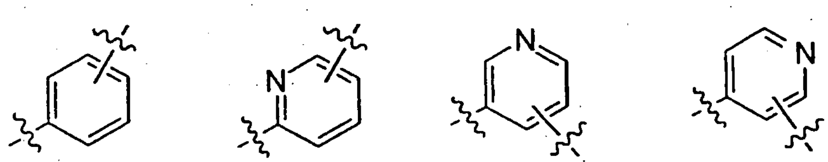


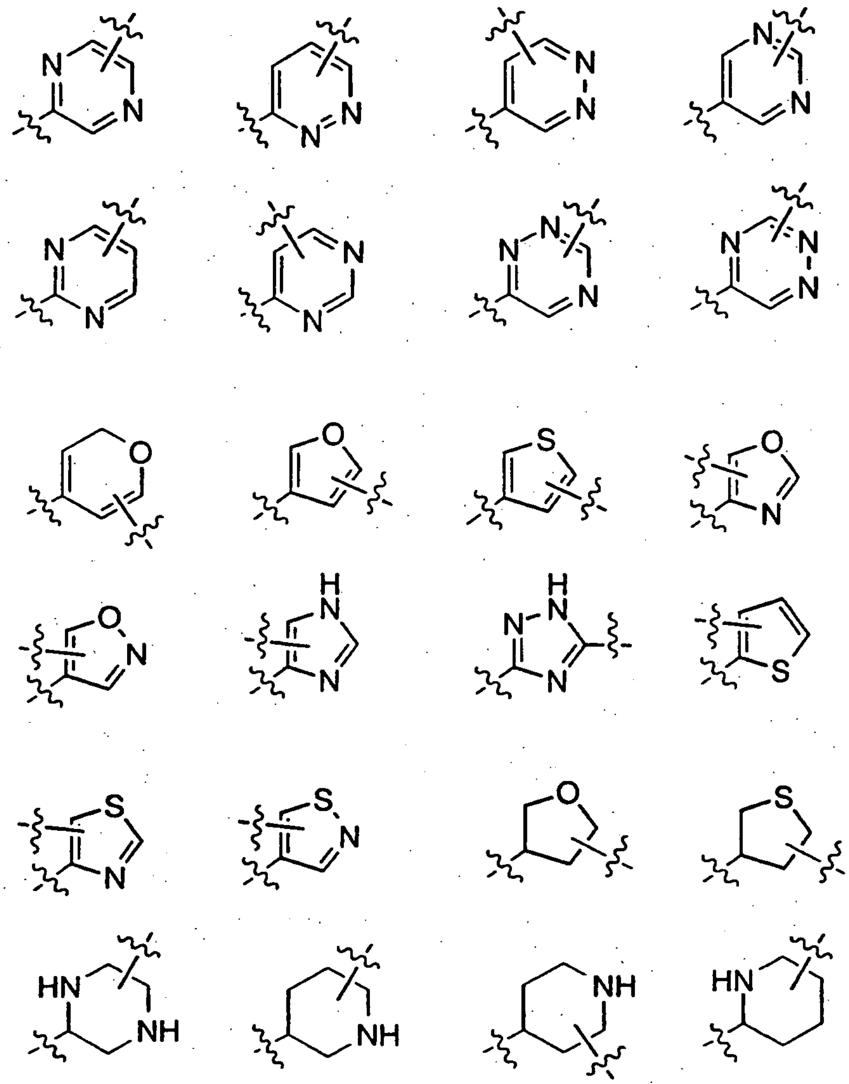
It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

With respect to the farnesyl-protein transferase inhibitors of the formula II, the substituent illustrated by the structure:

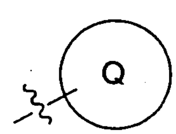


represents a 5, 6 or 7 membered carbocyclic ring wherein from 0 to 3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:



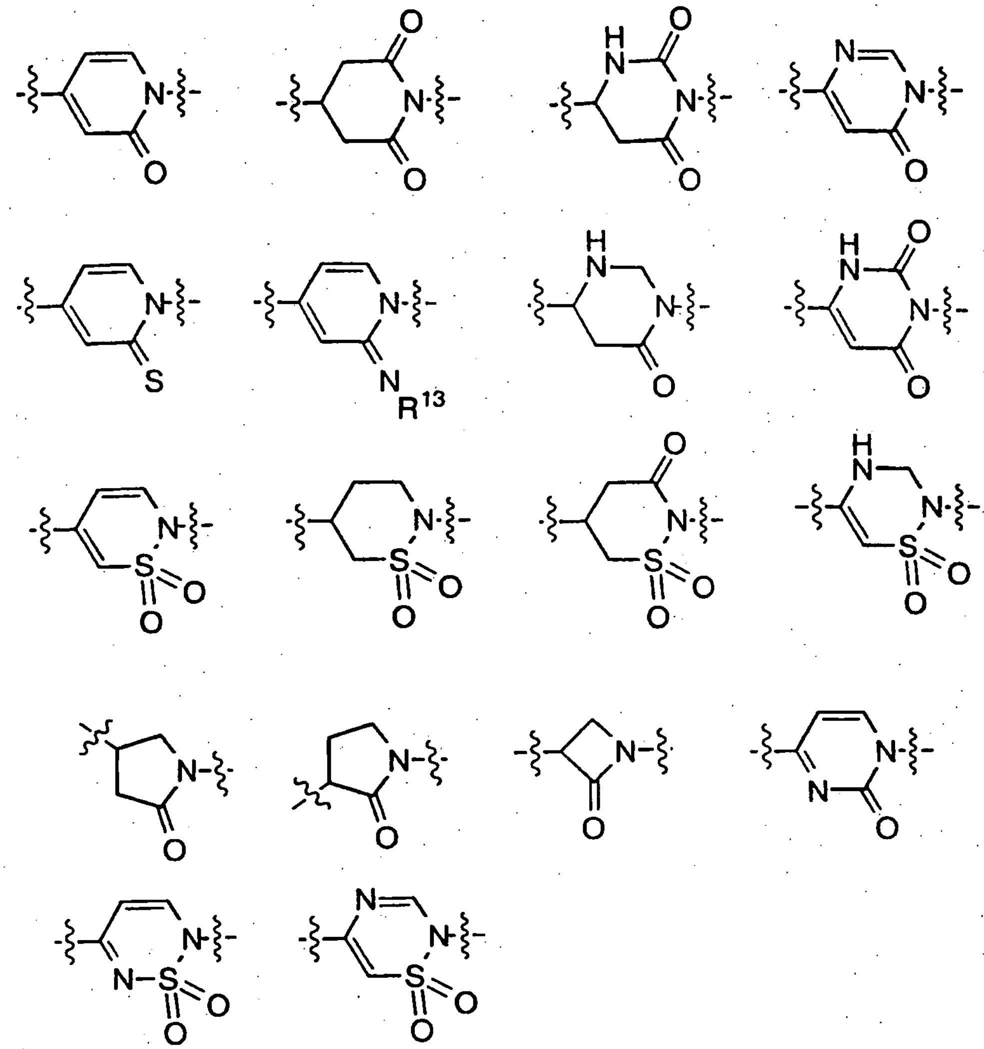


With respect to the farnesyl-protein transferase inhibitors of the formula III, the substituent illustrated by the structure:

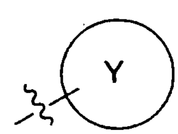


represents a 4, 5, 6 or 7 membered heterocyclic ring which comprises a nitrogen atom through which Q is attached to Y and 0-2 additional heteroatoms selected from N, S and O, and which also comprises a

carbonyl, thiocarbonyl, -C(=NR^{13})- or sulfonyl moiety adjacent to the nitrogen atom attached to Y and includes the following ring systems:

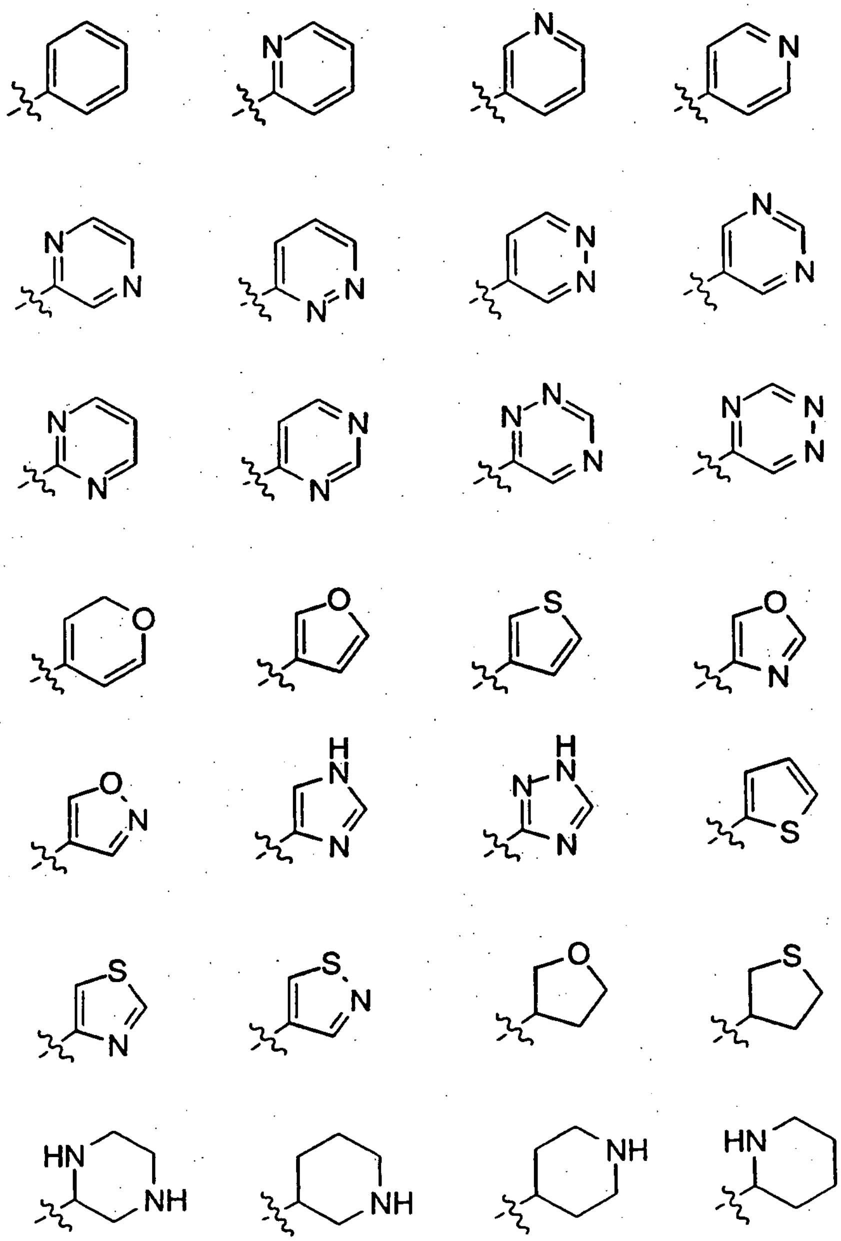


With respect to the farnesyl-protein transferase inhibitors of the formula III, the substituent illustrated by the structure:

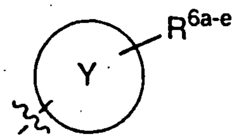


represents a 5-, 6- or 7-membered carbocyclic ring wherein from 0 to

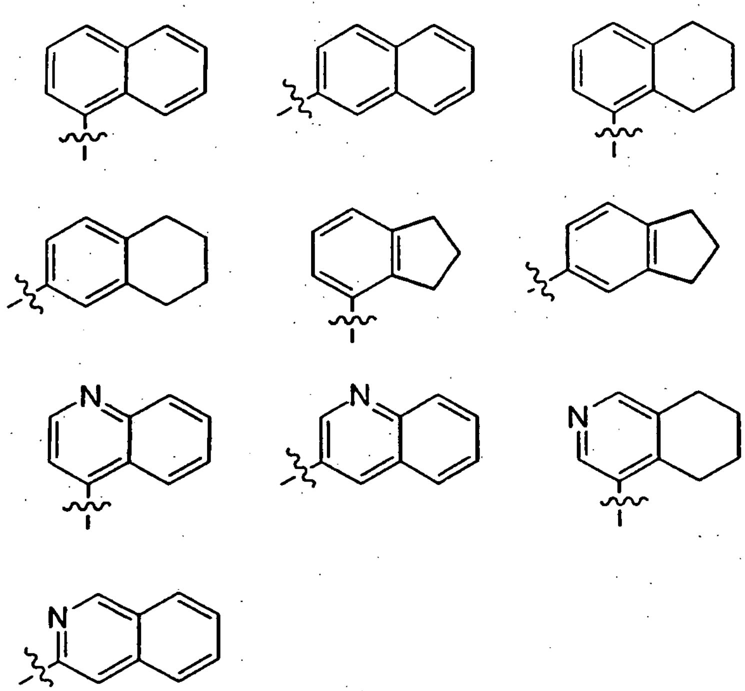
3 carbon atoms are replaced by a heteroatom selected from N, S and O, and wherein Y is attached to Q through a carbon atom and includes the following ring systems:



With respect to the farnesyl-protein transferase inhibitors of the formula III, the moiety described as



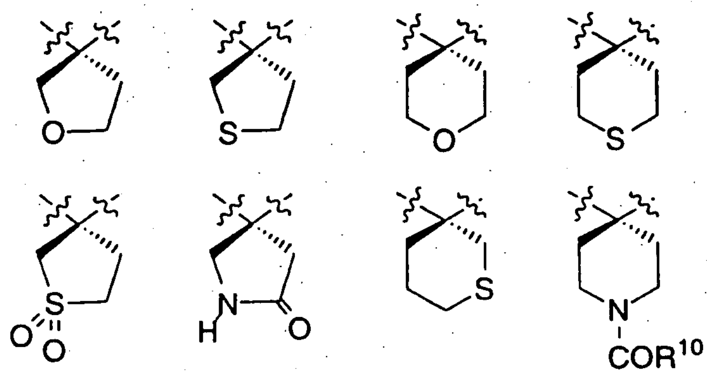
where any two of R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^{6e} on adjacent carbon atoms are combined to form a diradical selected from -CH=CH-CH=CH, -CH=CH-CH-, -(CH_2)4- and -(CH_2)4- includes, but is not limited to, the following structures:



It is understood that such fused ring moieties may be further substituted by the remaining R^{6a}, R^{6b}, R^{6c}, R^{6d} and/or R^{6e} as defined hereinabove.

When R^2, R^3 and other R^x substituents are combined to form - (CH_2)u -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenyl-acetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{10}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth below.

Peptidyl compounds that may be useful in the instantly claimed compositions can be synthesized from their constituent amino

acids by conventional peptide synthesis techniques, and the additional methods described below. Standard methods of peptide synthesis are disclosed, for example, in the following works: Schroeder *et al.*, *"The Peptides"*, Vol. I, Academic Press 1965, or Bodanszky *et al.*, *"Peptide Synthesis"*, Interscience Publishers, 1966, or McOmie (ed.) *"Protective Groups in Organic Chemistry"*, Plenum Press, 1973, or Barany *et al.*, *"The Peptides: Analysis, Synthesis, Biology"* 2, Chapter 1, Academic Press, 1980, or Stewart *et al.*, *"Solid Phase Peptide Synthesis"*, Second Edition, Pierce Chemical Company, 1984. Also useful in exemplifying syntheses of specific unnatural amino acid residues are European Pat. Appl. No. 0 350 163 A2 (particularly page 51-52) and J. E. Baldwin *et al. Tetrahedron*, 50:5049-5066 (1994). With regards to the synthesis of instant compounds containing a (β-acetylamino)alanine residue at the C-terminus, use of the commercially available Nα-Z-L-2,3-diaminopropionic acid (Fluka) as a starting material is preferred.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

Ac_2O	Acetic anhydride;
Boc	t-Butoxycarbonyl;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
DMAP	4-Dimethylaminopyridine;
DME	1,2-Dimethoxyethane;
DMF	Dimethylformamide;
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
HOBT	1-Hydroxybenzotriazole hydrate;
Et_3N	Triethylamine;
EtOAc	Ethyl acetate;
FAB	Fast atom bombardment;
HOOBT	3-Hydroxy-1,2,2-benzotriazin-4(3*H*)-one;
HPLC	High-performance liquid chromatography;
MCPBA	m-Chloroperoxybenzoic acid;
MsCl	Methanesulfonyl chloride;

NaHMDS	Sodium bis(trimethylsilyl)amide;
Py	Pyridine;
TFA	Trifluoroacetic acid;
THF	Tetrahydrofuran.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds useful in the instant invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The inhibitors of farnesyl-protein transferase of formula (I-b') can be synthesized in accordance with Schemes 1-11, in addition to other standard manipulations such as ester hydrolysis, cleavage of

protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; however their point of attachment to the ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-11:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part.

Piperazin-5-ones can be prepared as shown in Scheme 1. Thus, the protected suitably substituted amino acid IV can be converted to the corresponding aldehyde V by first forming the amide and then reducing it with LAH. Reductive amination of Boc-protected amino aldehydes V gives rise to compound VI. The intermediate VI can be converted to a piperazinone by acylation with chloroacetyl chloride to give VII, followed by base-induced cyclization to VIII. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to IX, which can be alkylated with an arylmethylhalide to give the imidazolium salt X. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product XI.

The intermediate VIII can be reductively alkylated with a variety of aldehydes, such as XII. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 2). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent

such as dichloroethane, methanol or dimethylformamide. The product XIII can be deprotected to give the final compounds XIV with trifluoroacetic acid in methylene chloride. The final product XIV is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XIV can further be selectively protected to obtain XV, which can subsequently be reductively alkylated with a second aldehyde to obtain XVI. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XVII can be accomplished by literature procedures.

Alternatively, the imidazole acetic acid XVIII can be converted to the acetate XIX by standard procedures, and XIX can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XX (Scheme 3). Hydrolysis and reaction with piperazinone VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXI.

If the piperazinone VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXII in Scheme 4, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 4, 5). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIV. In addition, the fully deprotected amino alcohol XXV can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXVI (Scheme 5), or tertiary amines.

The Boc protected amino alcohol XXIII can also be utilized to synthesize 2-aziridinylmethylpiperazinones such as XXVII (Scheme 6). Treating XXIII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXVII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXVIII.

In addition, the piperazinone VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines,

according to standard procedures, to obtain compounds such as XXX (Scheme 7). When R' is an aryl group, XXX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXI. Alternatively, the amine protecting group in XXX can be removed, and O-alkylated phenolic amines such as XXXII produced.

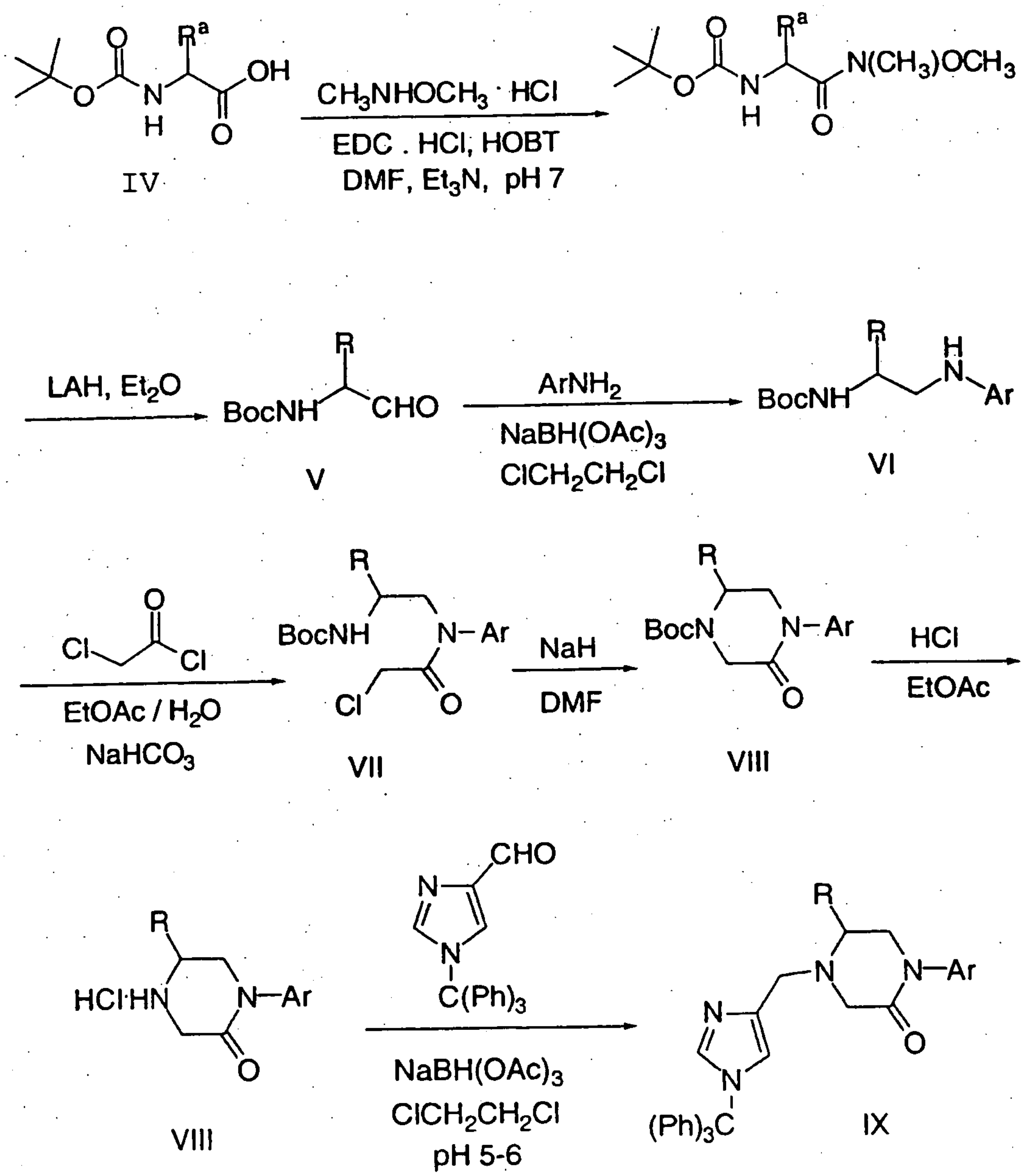
Scheme 8 illustrates the use of an optionally substituted homoserine lactone XXXIII to prepare a Boc-protected piperazinone XXXVII. Intermediate XXXVII may be deprotected and reductively alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of intermediate XXXVII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate XXXVIII. Intermediate XXXVII may also be oxidized to provide the carboxylic acid on intermediate IXL, which can be utilized form an ester or amide moiety.

N-Aralkyl-piperazin-5-ones can be prepared as shown in Scheme 9. Reductive amination of Boc-protected amino aldehydes V (prepared from III as described previously) gives rise to compound XL. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide to give XLI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 1-7.

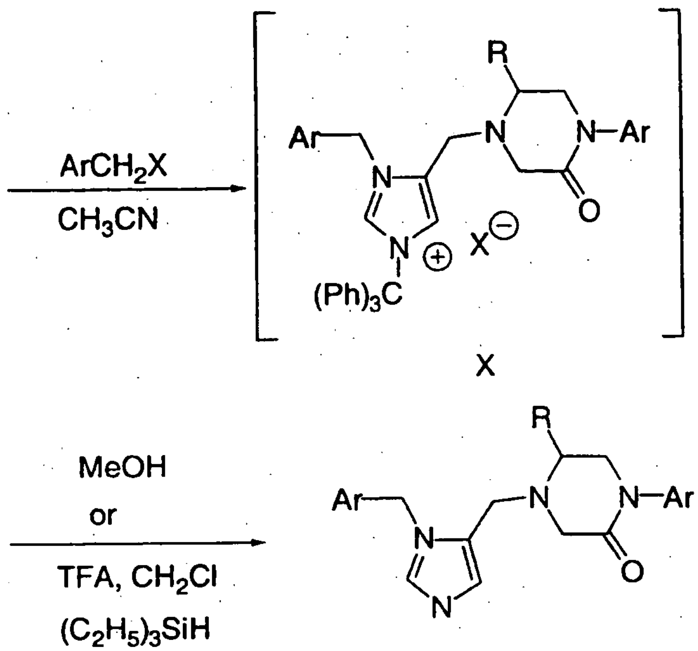
The isomeric piperazin-3-ones can be prepared as described in Scheme 10. The imine formed from arylcarboxamides XLII and 2-aminoglycinal diethyl acetal (XLIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine XLIV. Amino acids I can be coupled to amines XLIV under standard conditions, and the resulting amide XLV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated XLVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate XLVII, which is elaborated to final products as described in Schemes 1-7.

Amino acids of the general formula IL which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 11 starting with the readily prepared imine XLVIII.

SCHEME 1



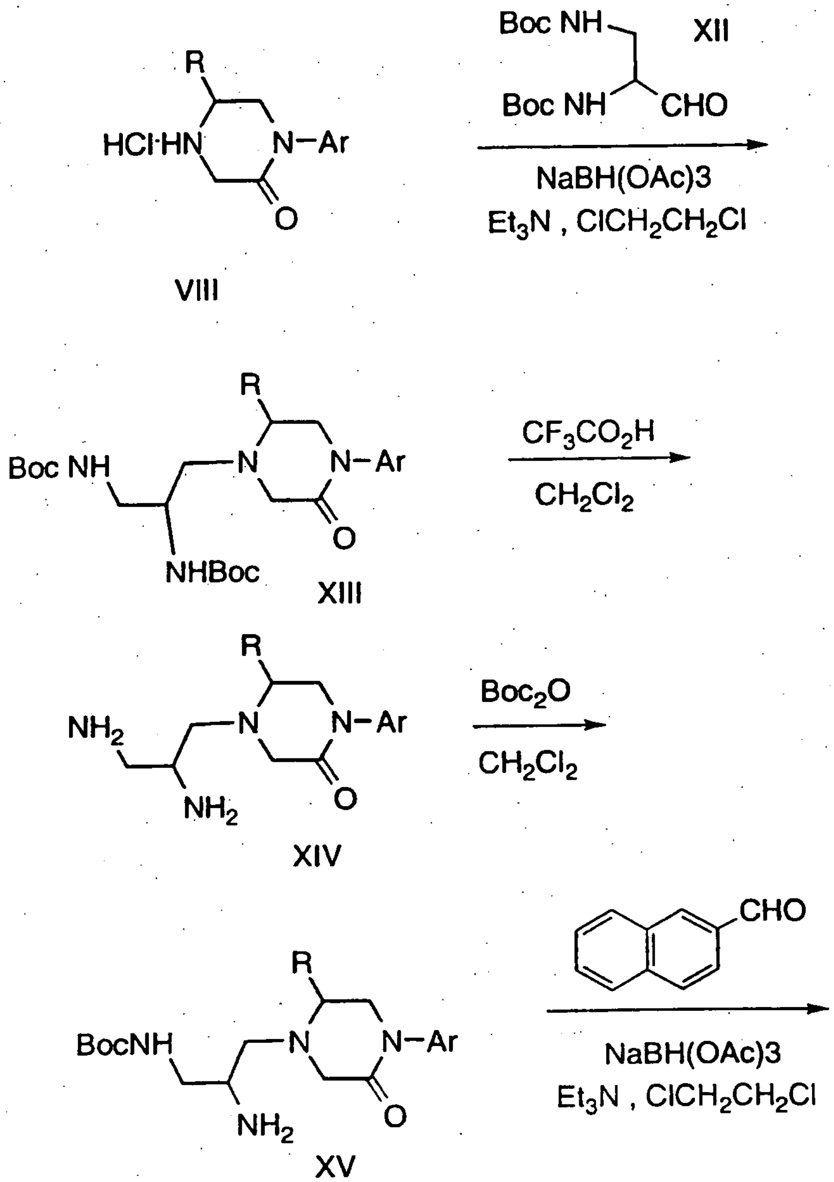
SCHEME 1 (continued)



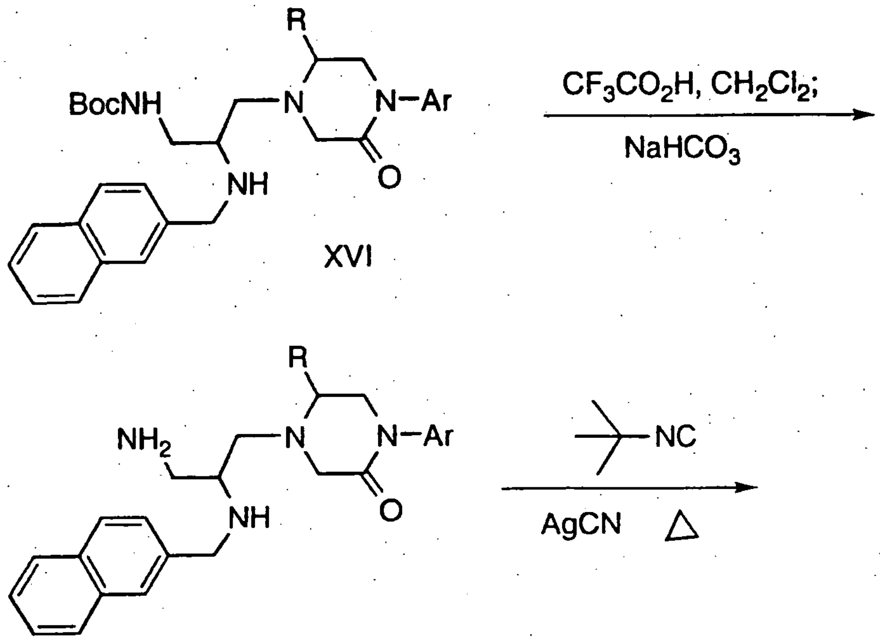
X

XI

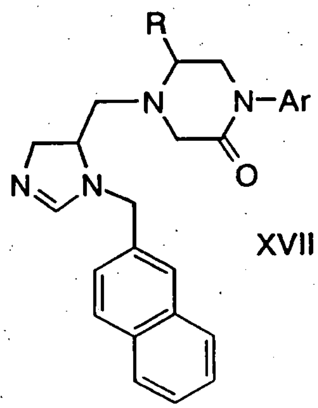
SCHEME 2


Boc NH
XII
Boc NH
CHO
R
HCl·HN
N−Ar
O
NaBH(OAc)3
Et3N , ClCH2CH2Cl
VIII
R
Boc NH
N
N−Ar
O
NHBoc
XIII
CF3CO2H
CH2Cl2
R
NH2
N
N−Ar
NH2
O
XIV
Boc2O
CH2Cl2
CHO
R
BocNH
N
N−Ar
NH2
O
XV
NaBH(OAc)3
Et3N , ClCH2CH2Cl

SCHEME 2 (continued)

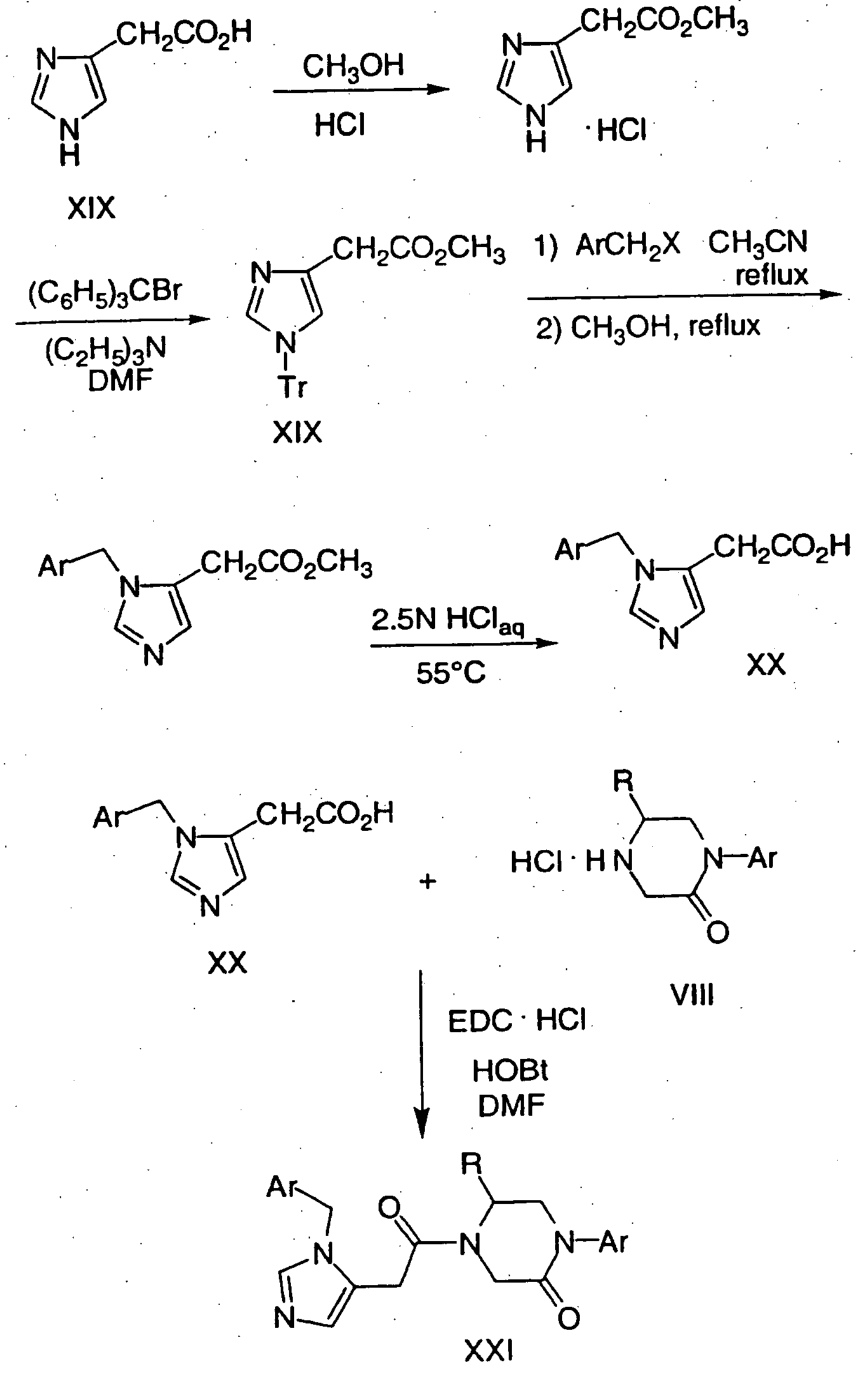


XVI

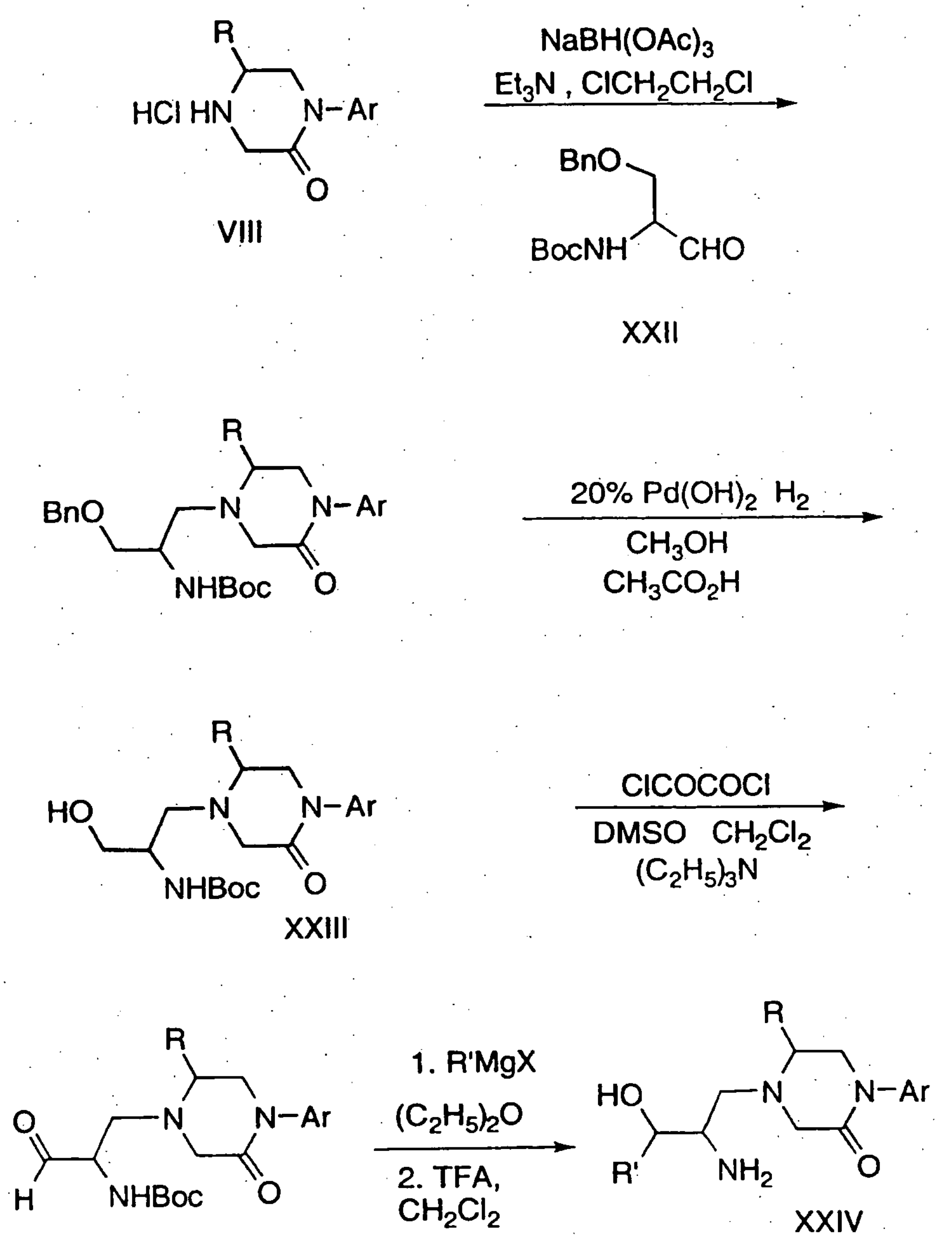


XVII

SCHEME 3

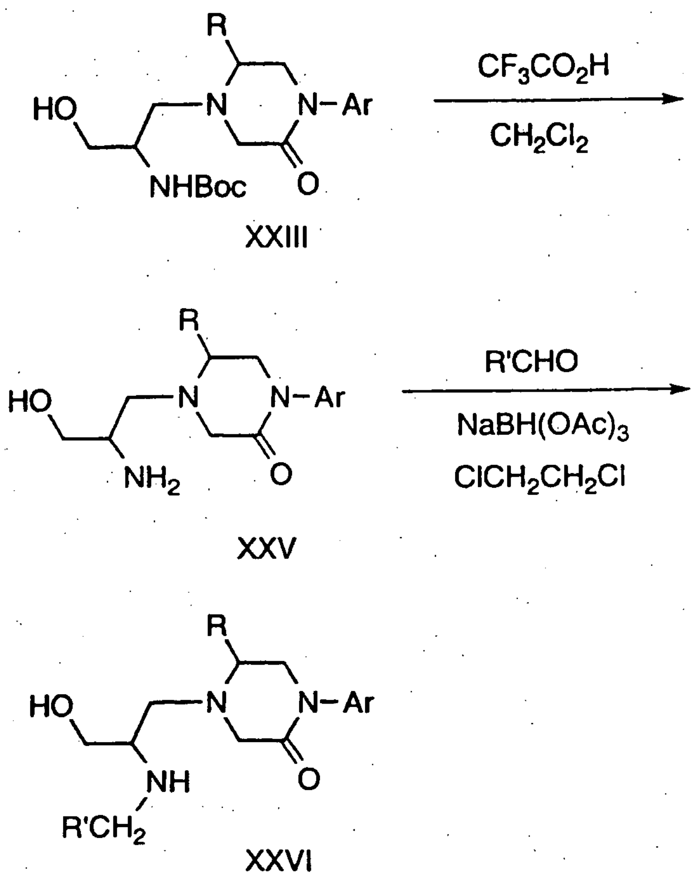

CH3OH
HCl
XIX
(C6H5)3CBr
(C2H5)3N
DMF
XIX
1) ArCH2X CH3CN reflux
2) CH3OH, reflux
2.5N HClaq
55°C
XX
+
XX
VIII
EDC · HCl
HOBt
DMF
XXI

SCHEME 4

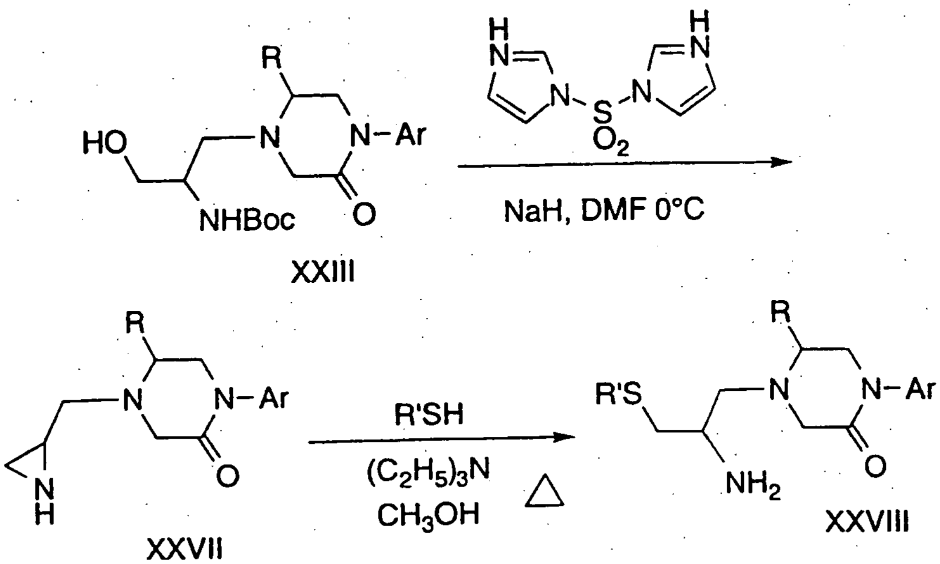


R
HCl HN
N-Ar
O
VIII
NaBH(OAc)3
Et3N , ClCH2CH2Cl
BnO
BocNH
CHO
XXII
BnO
N
N-Ar
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
HO
NHBoc
XXIII
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
H
1. R'MgX
(C2H5)2O
2. TFA,
CH2Cl2
R'
NH2
XXIV

SCHEME 5


R
HO
N
N-Ar
NHBoc
O
XXIII
CF_3CO_2H
CH_2Cl_2
R
HO
N
N-Ar
NH_2
O
XXV
R'CHO
$NaBH(OAc)_3$
$ClCH_2CH_2Cl$
R
HO
N
N-Ar
NH
$R'CH_2$
O
XXVI

SCHEME 6

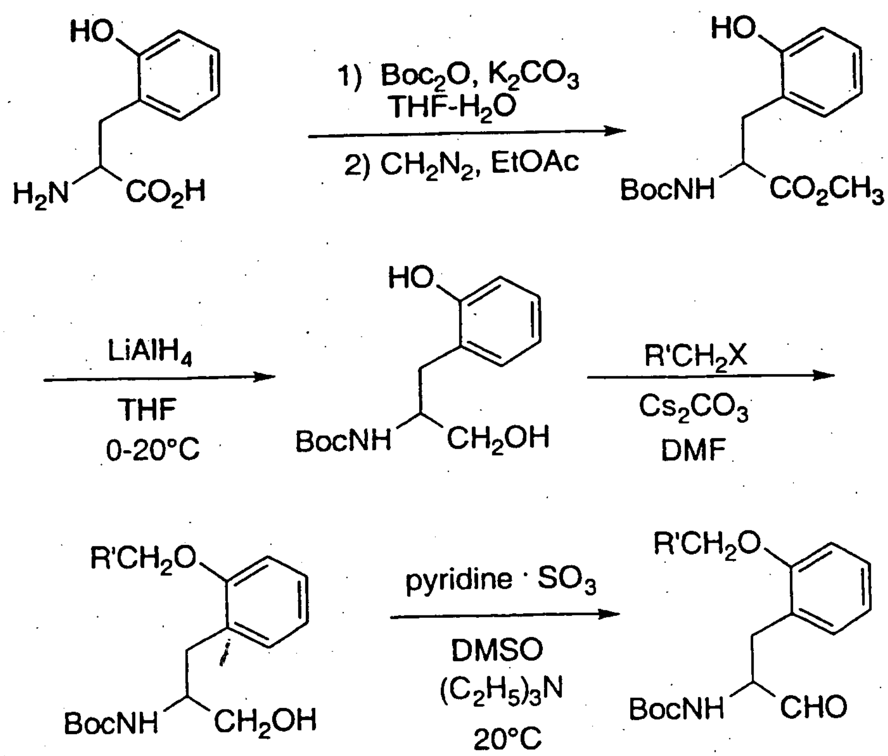


XXIII

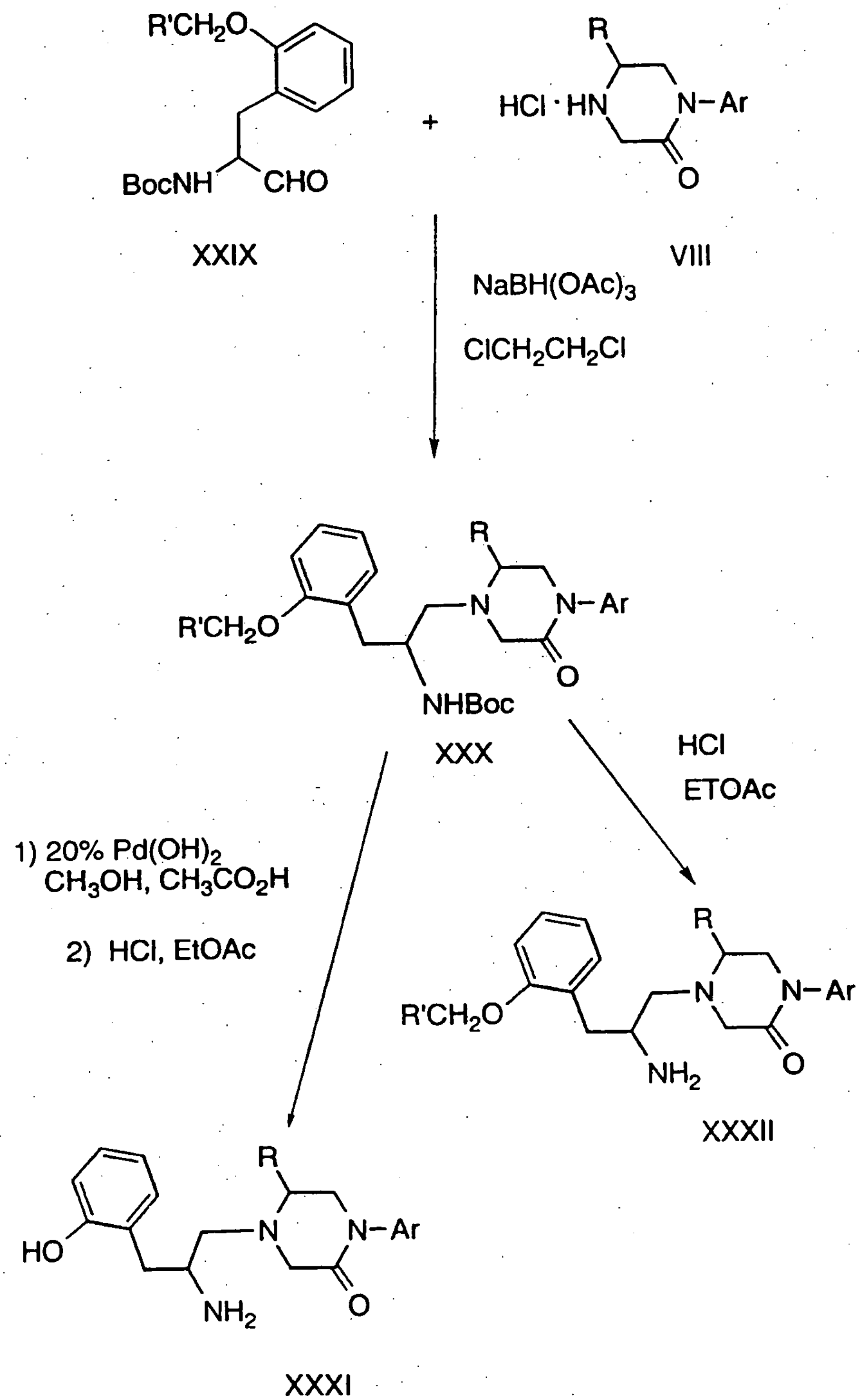
XXVII

XXVIII

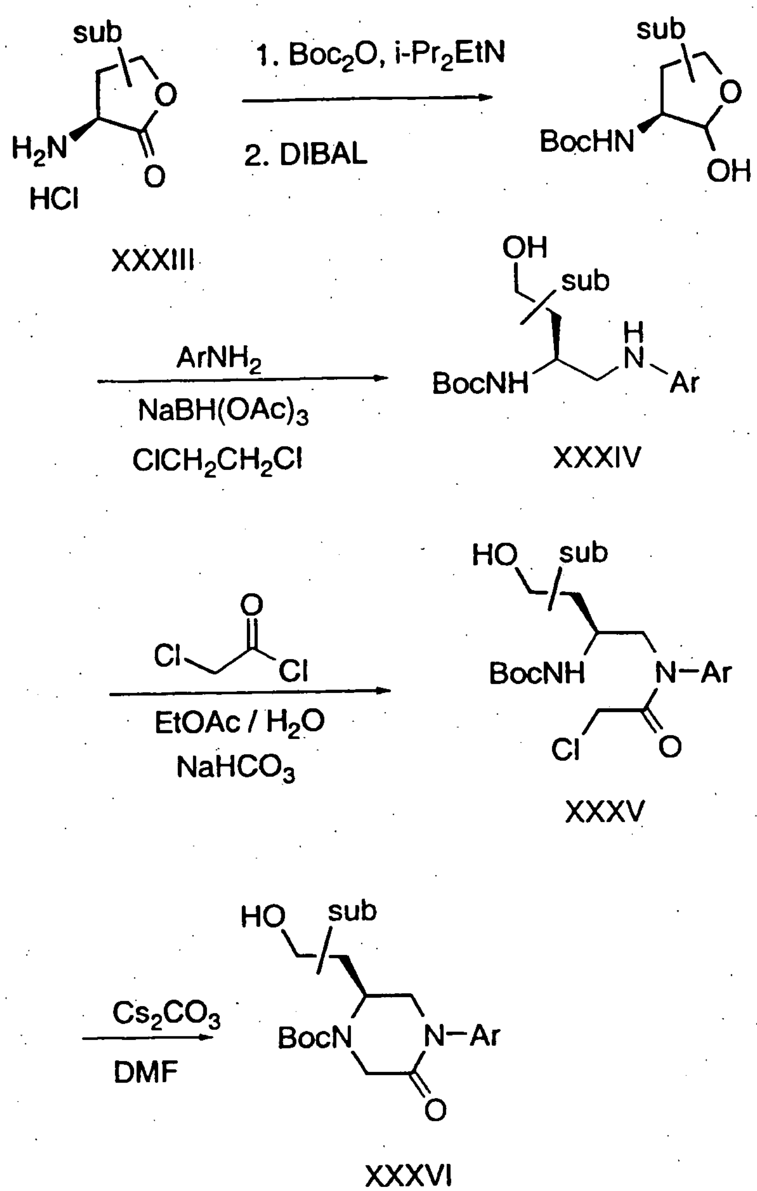
SCHEME 7



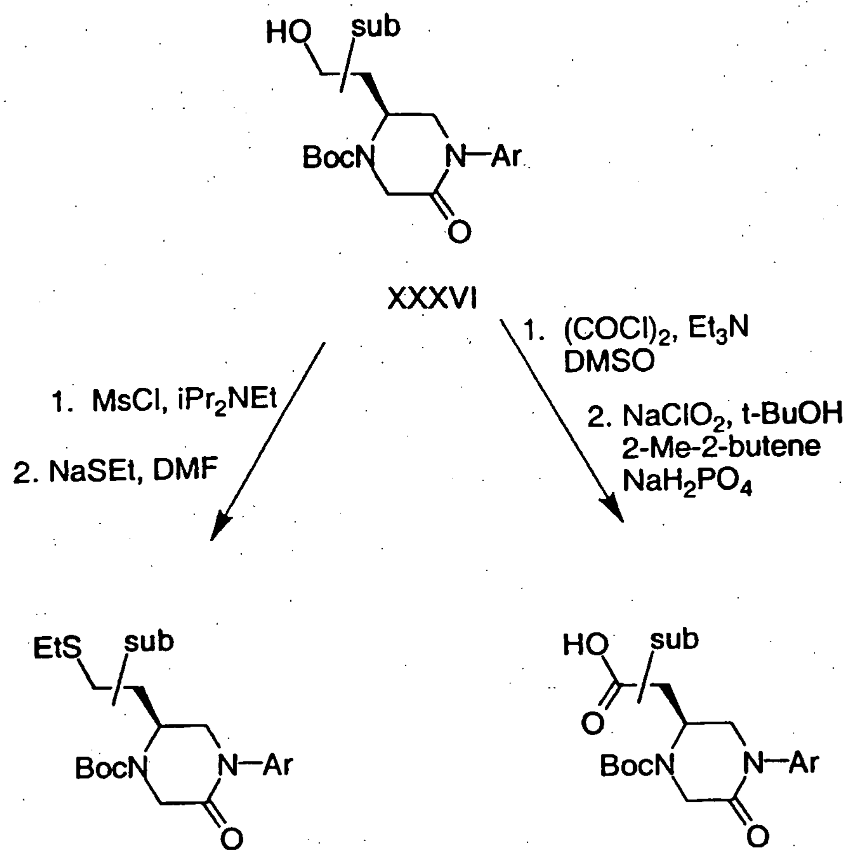
SCHEME 7 (continued)



SCHEME 8


sub
H2N
HCl
1. Boc2O, i-Pr2EtN
2. DIBAL
BocHN
OH
XXXIII
ArNH2
NaBH(OAc)3
ClCH2CH2Cl
BocNH
Ar
XXXIV
EtOAc / H2O
NaHCO3
XXXV
Cs2CO3
DMF
BocN
N–Ar
XXXVI

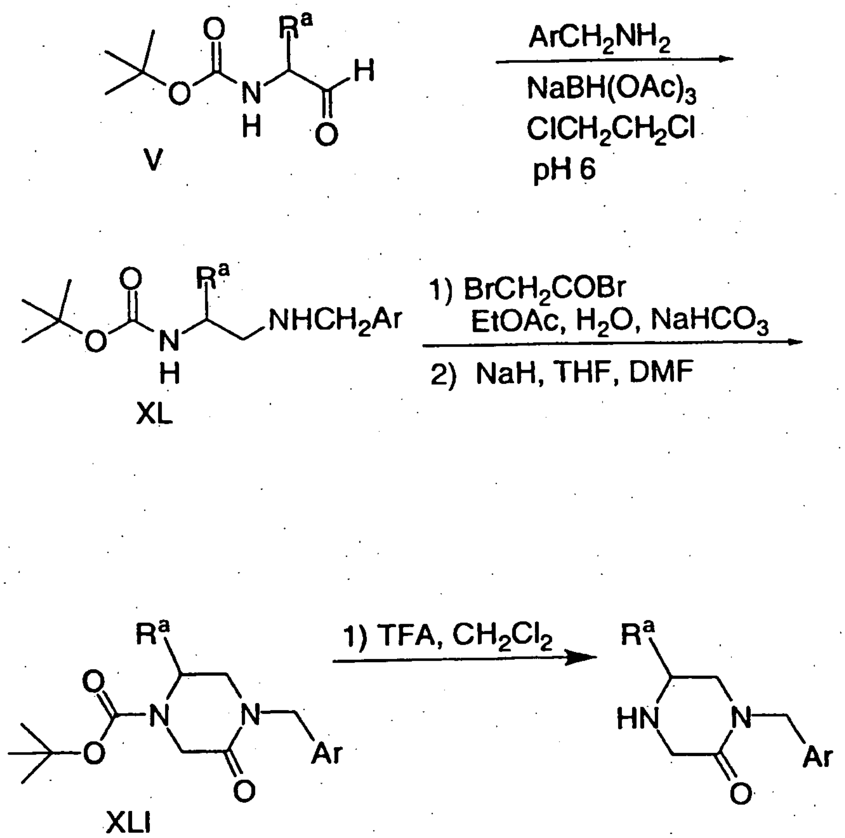
SCHEME 8 (continued)



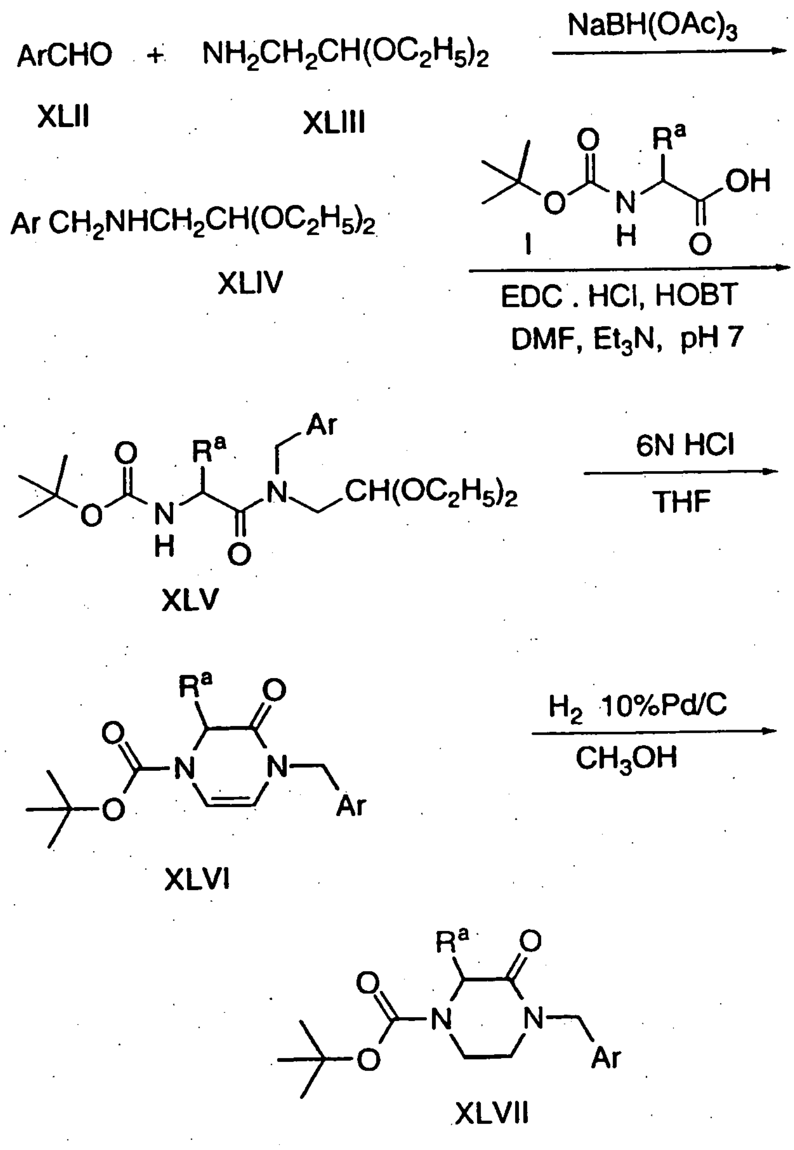
XXXVIII

IXL

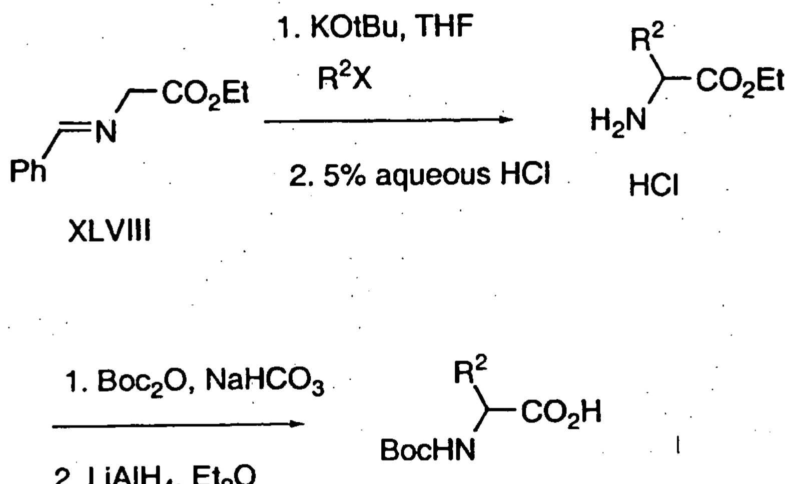
SCHEME 9


V
XL
XLI
$ArCH_2NH_2$
$NaBH(OAc)_3$
$ClCH_2CH_2Cl$
pH 6
1) $BrCH_2COBr$
EtOAc, H_2O, $NaHCO_3$
2) NaH, THF, DMF
1) TFA, CH_2Cl_2
NHCH$_2$Ar
HN
Ar
R^a

SCHEME 10


ArCHO + $NH_2CH_2CH(OC_2H_5)_2$
NaBH(OAc)3
XLII
XLIII
Ar $CH_2NHCH_2CH(OC_2H_5)_2$
XLIV
I
EDC . HCl, HOBT
DMF, Et3N, pH 7
XLV
6N HCl
THF
XLVI
H2 10%Pd/C
CH3OH
XLVII

SCHEME 11



XLVIII

IL

Reactions used to generate the compounds of the formula (VI) are prepared by employing reactions as shown in the Schemes 12-33, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; substituent "sub" represents a suitable substituent on the substituent Z. The point of attachment of such substituents to a ring is illustrative only and is not meant to be limiting.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 12-33:

The requisite intermediates utilized as starting material in the Schemes hereinbelow are in some cases commercially available, or can be prepared according to literature procedures. In Scheme 12, for example, a suitably substituted Boc protected isonipecotate LI may

be deprotonated and then treated with a suitably substituted alkylating group, such as a suitably substituted benzyl bromide, to provide the gem disubstituted intermediate LIII. Deprotection and reduction provides the hydroxymethyl piperidine LIV which can be utilized is synthesis of compounds of the invention or which may be nitrogen-protected and methylated to give the intermediate LV.

As shown in Scheme 13, the protected piperidine intermediate LIII can be deprotected and reductively alkylated with aldehydes such as 1-trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as LVI. The trityl protecting group can be removed from LVI to give LVII, or alternatively, LVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole LVIII.

The deprotected intermediate LIII can also be reductively alkylated with a variety of other aldehydes and acids as shown above in Schemes 4-7.

An alternative synthesis of the hydroxymethyl intermediate LIV and utilization of that intermediate in the synthesis of the instant compounds which incorporate the preferred imidazolyl moiety is illustrated in Scheme 14. Scheme 15 illustrates the reductive alkylation of intermediate LIV to provide a 4-cyanobenzylimidazolyl substituted piperidine. The cyano moiety may be selectively hydrolyzed with sodium borate to provide the corresponding amido compound of the instant invention.

Scheme 16 alternative preparation of the methyl ether intermediate LV and the alkylation of LV with a suitably substituted imidazolylmethyl chloride to provide the instant compound. Preparation of the homologous 1-(imidazolylethyl)piperidine is illustrated in Scheme 17.

Specific substitution on the piperidine of the compounds of the instant invention may be accomplished as illustrated in Scheme 18. Thus, metal-halogen exchange coupling of a butynyl moiety to an isonicotinate, followed by hydrogenation, provides the 2-butylpiperidine intermediate that can then undergo the reactions previously described

to provide the compound of the instant invention.

Incorporation of a 4-amido moiety for LV is illustrated in Scheme 19.

Scheme 20 illustrates the synthesis of the instant compounds wherein the moiety Z is attached directly to the piperidine ring. Thus the piperidone LIX is treated with a suitably substituted phenyl Grignard reagent to provide the gem disubstituted piperidine LX. Deprotection provides the key intermediate LXI. Intermediate LXI may be acetylated as described above to provide the instant compound LXII (Scheme 21).

As illustrated in Scheme 22, the protected piperidine LX may be dehydrated and then hydroborated to provide the 3-hydroxypiperidine LXIII. This compound may be deprotected and further derivatized to provide compounds of the instant invention (as shown in Scheme 23) or the hydroxyl group may be alkylated, as shown in Scheme 22, prior to deprotection and further manipulation.

The dehydration product may also be catalytically reduced to provide the des-hydroxy intermediate LXV, as shown in Scheme 24, which can be processed via the reactions illustrated in the previous Schemes.

Schemes 25 and 26 illustrate further chemical manipulations of the 4-carboxylic acid functionality to provide instant compounds wherein the substituent Y is an acetylamine or sulfonamide moiety.

Scheme 27 illustrates incorporation of a nitrile moiety in the 4-position of the piperidine of the compounds of formula II. Thus, the hydroxyl moiety of a suitably substituted 4-hydroxypiperidine is substituted with nitrile to provide intermediate LXVI, which can undergo reactions previously described in Schemes 17-21.

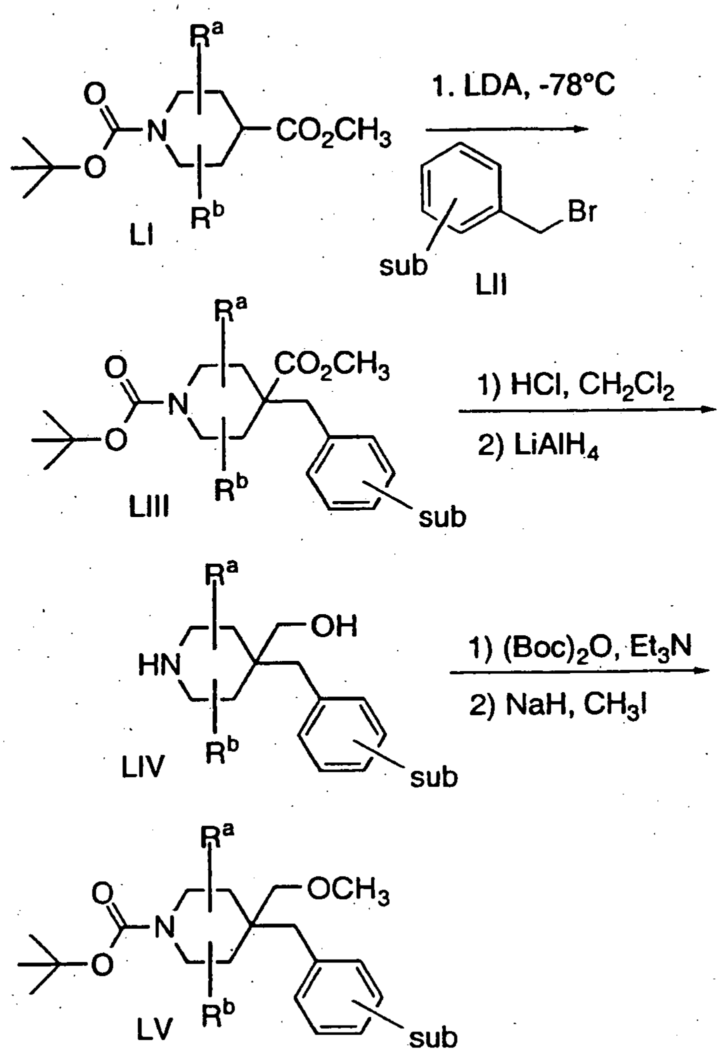
Scheme 28 illustrates the preparation of several pyridyl intermediates that may be utilized with the piperidine intermediates such as compound LI in Scheme 16 to provide the instant compounds. Scheme 29 shows a generalized reaction sequence which utilizes such pyridyl intermediates.

Compounds of the instant invention wherein X^1 is a carbonyl moiety may be prepared as shown in Scheme 30. Intermediate LXVII may undergo subsequent reactions as illustrated in Schemes 13-17 to provide the instant compounds. Preparation of the instant compounds wherein X^1 is sulfur in its various oxidation states is shown in Scheme 31. Intermediates LXVIII-LXXI may undergo the previously described reactions to provide the instant compounds.

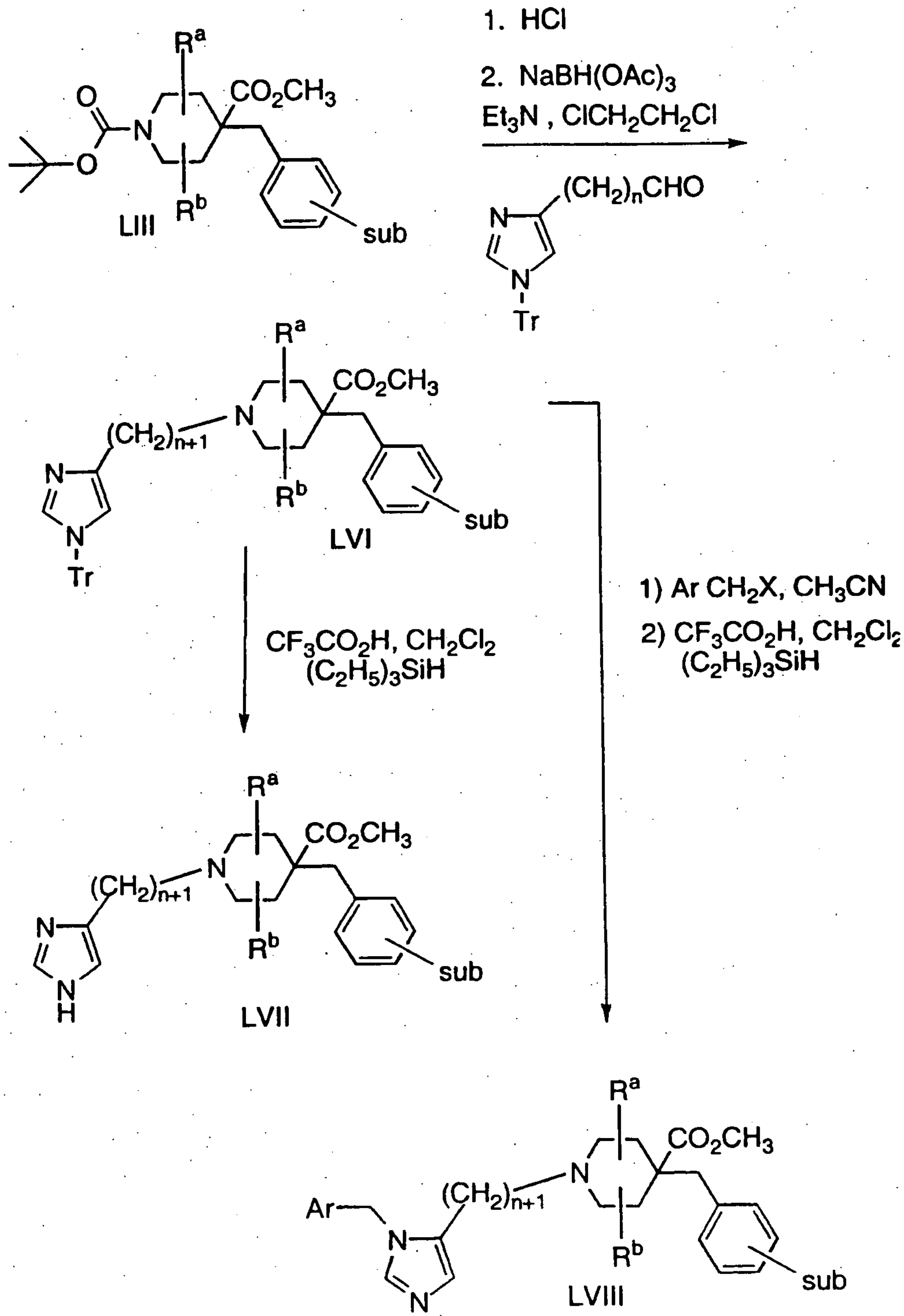
Scheme 32 illustrated preparation of compounds of the formula A wherein Y is hydrogen. Thus, suitably substituted isonipecotic acid may be treated with N,O-dimethylhydroxylamine and the intermediate LXXII reacted with a suitably substituted phenyl Grignard reagent to provide intermediate LXXIII. That intermediate may undergo the reactions previously described in Schemes 13-17 and may be further modified by reduction of the phenyl ketone to provide the alcohol LXXIV.

Compounds of the instant invention wherein X^1 is an amine moiety may be prepared as shown in Scheme 33. Thus the N-protected 4-piperidinone may be reacted with a suitably substituted aniline in the presence of trimethylsilylcyanide to provide the 4-cyano-4-aminopiperidine LXXV. Intermediate LXXV may then be converted in sequence to the corresponding amide LXXVI, ester LXXVII and alcohol LXXVIII. Intermediates LXXVI-LXXVIII can be deprotected and can then undergo the reactions previously described in Schemes 13-17 to provide the compounds of the instant invention.

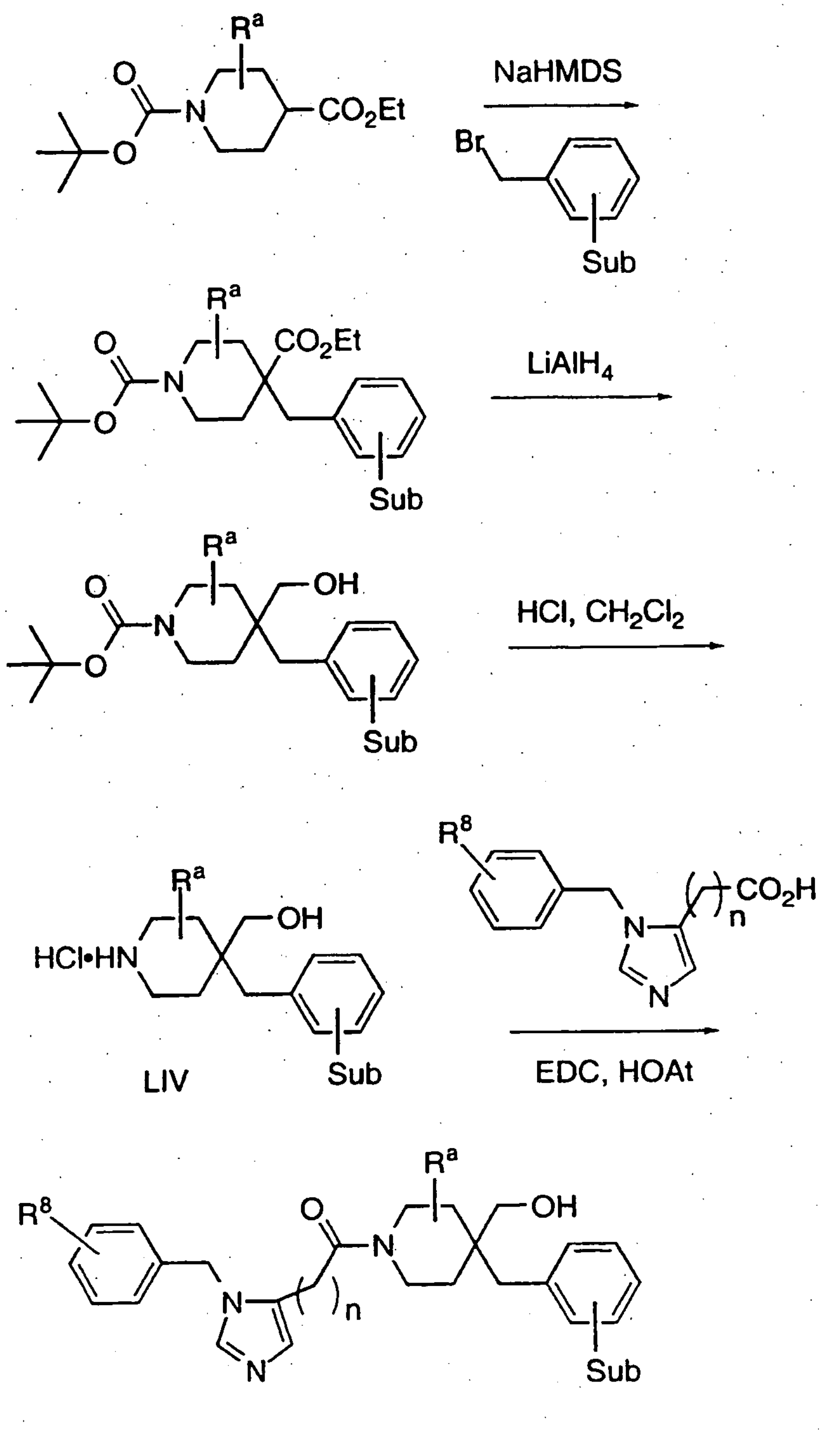
SCHEME 12



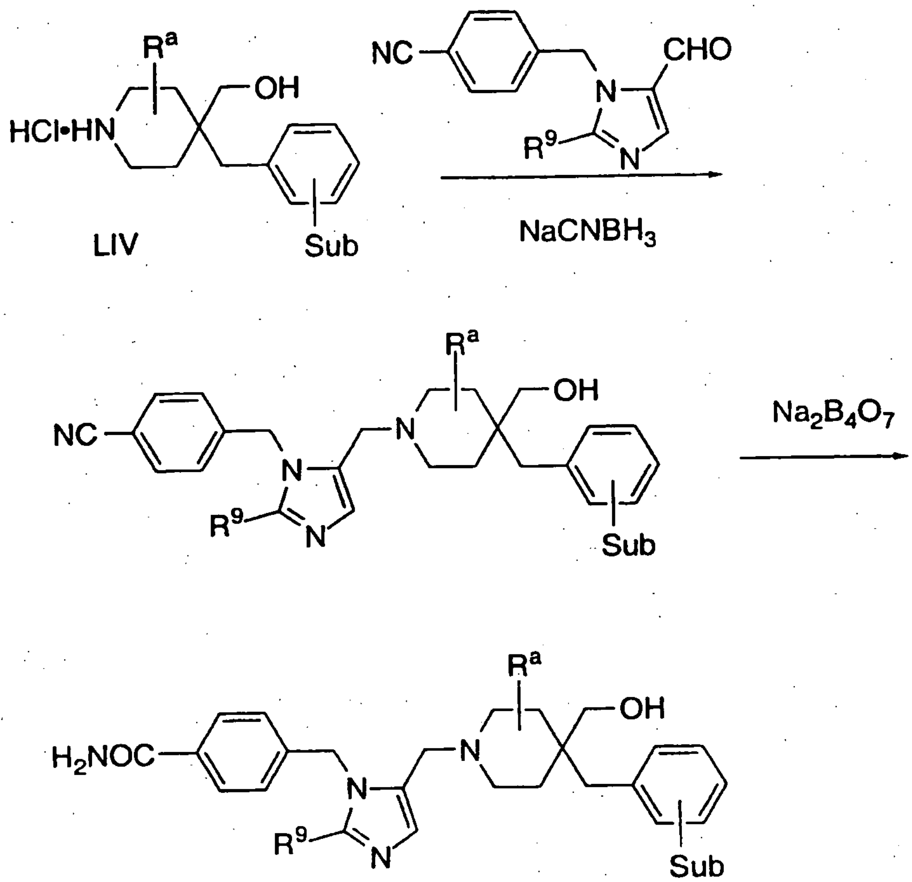
SCHEME 13


1. HCl
2. NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
Tr
LIII
LVI
LVII
LVIII
CF3CO2H, CH2Cl2
(C2H5)3SiH
1) Ar CH2X, CH3CN
2) CF3CO2H, CH2Cl2
(C2H5)3SiH
CO2CH3
sub
Ar

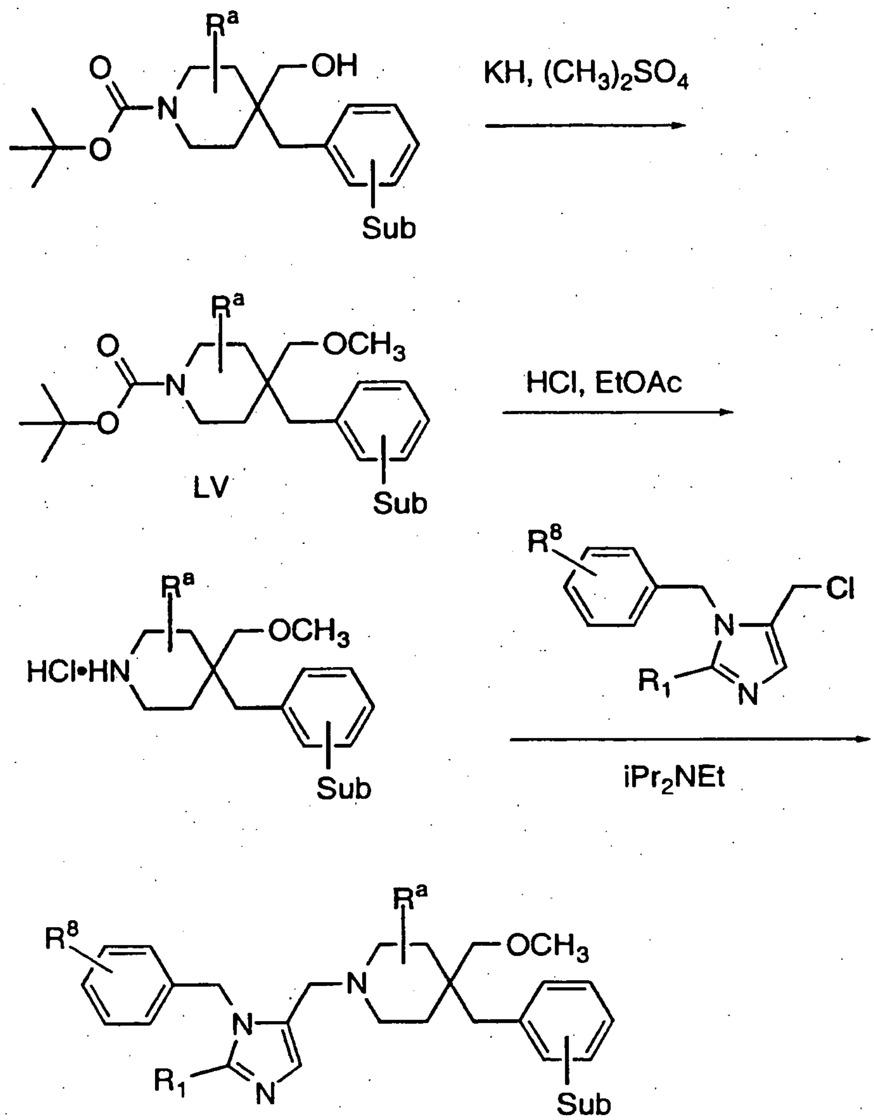
SCHEME 14



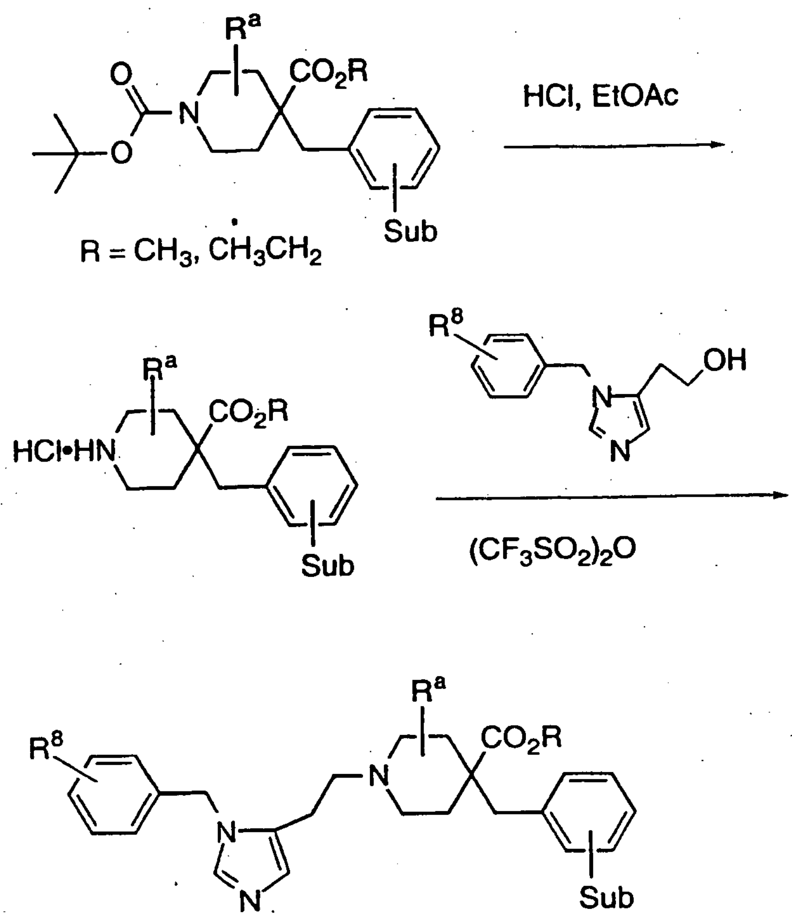
SCHEME 15



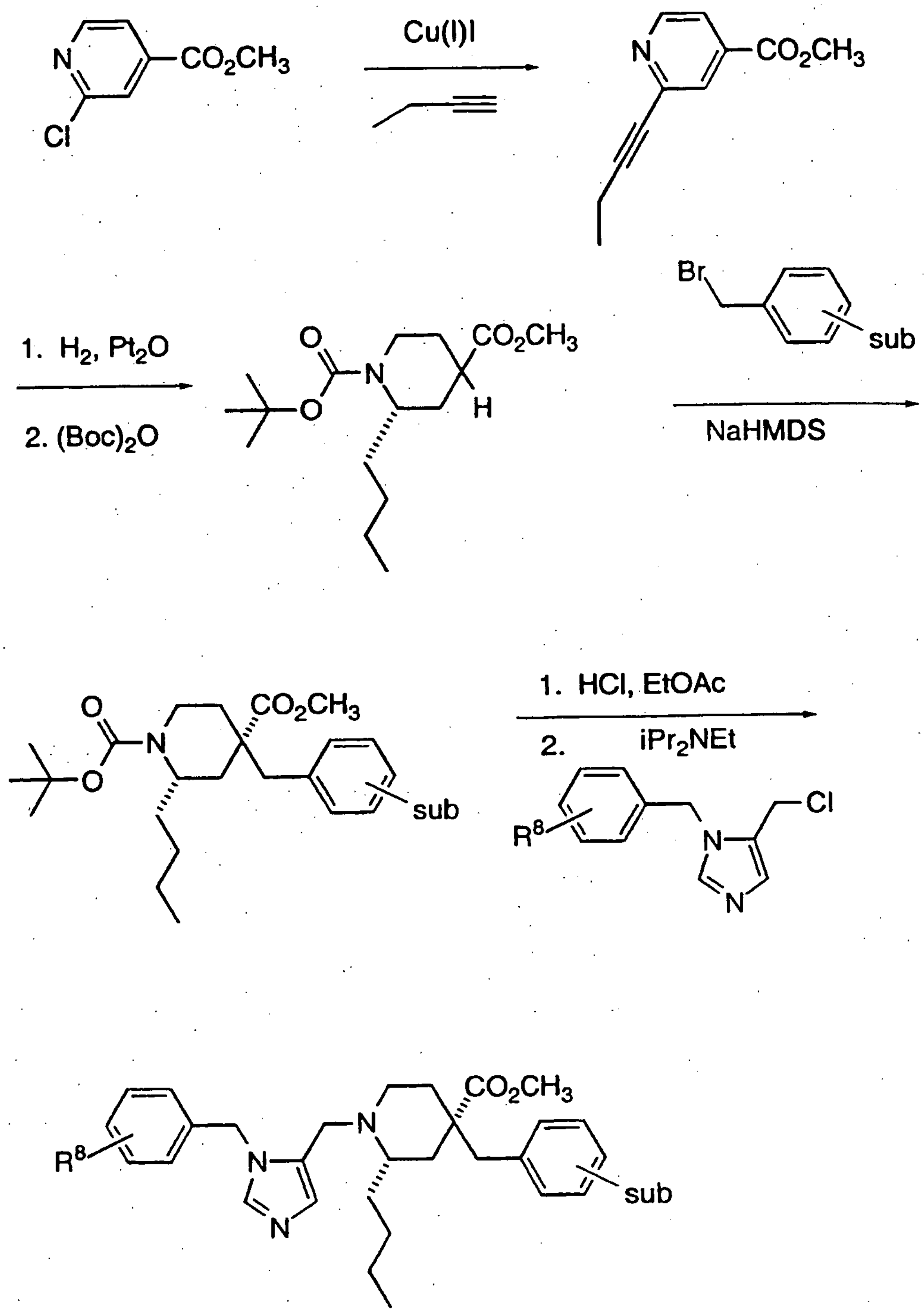
SCHEME 16



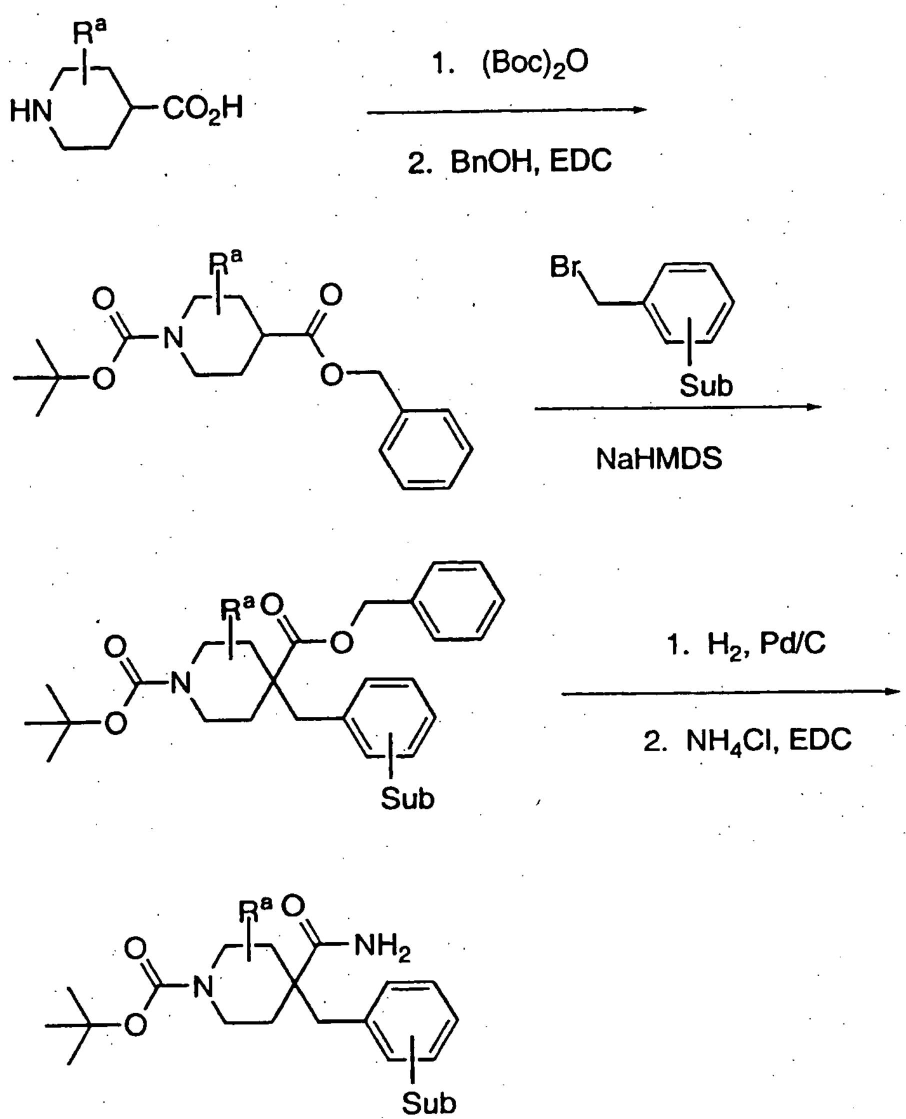
SCHEME 17



SCHEME 18

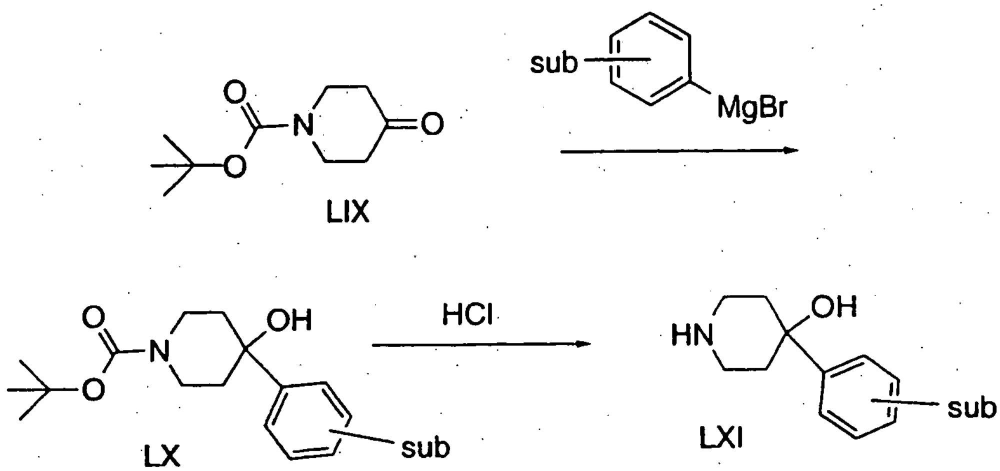

CO2CH3
N
Cl
Cu(I)I
1. H2, Pt2O
2. (Boc)2O
Br
sub
NaHMDS
H
O
1. HCl, EtOAc
2. iPr2NEt
R8
Cl

SCHEME 19

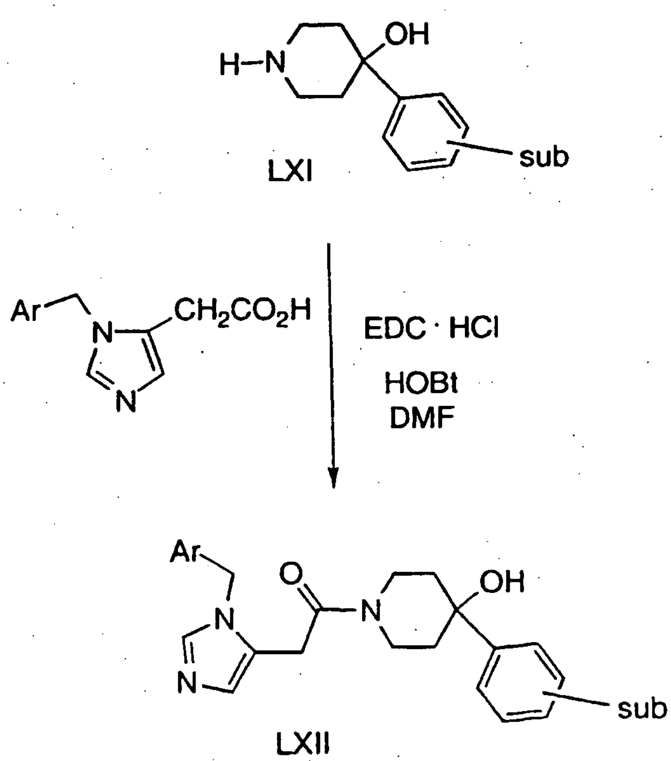


Ra
HN
CO2H
1. (Boc)2O
2. BnOH, EDC
O
N
O
Br
Sub
NaHMDS
1. H2, Pd/C
2. NH4Cl, EDC
NH2

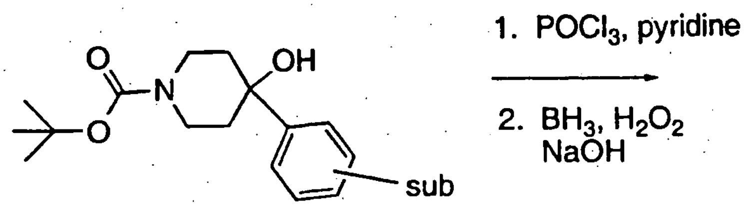
SCHEME 20



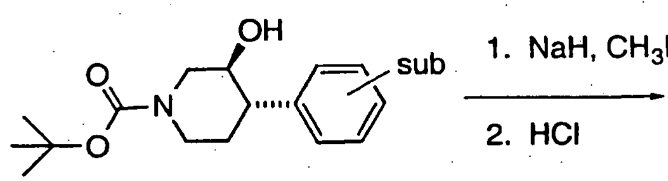
SCHEME 21



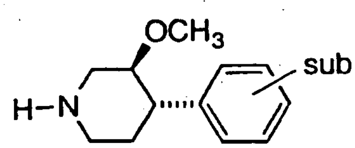
SCHEME 22



LX

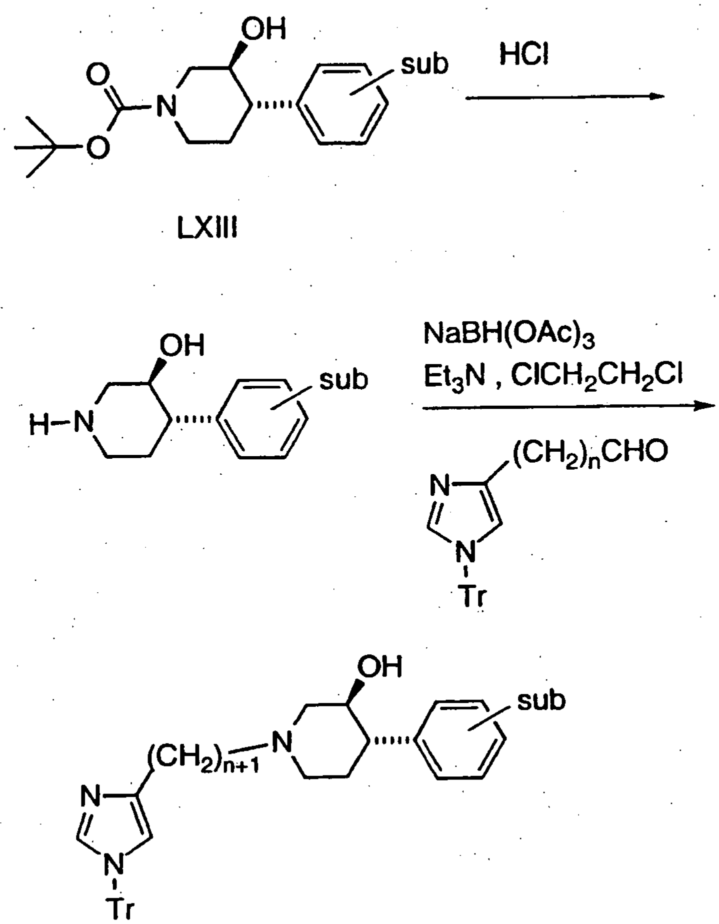


LXIII

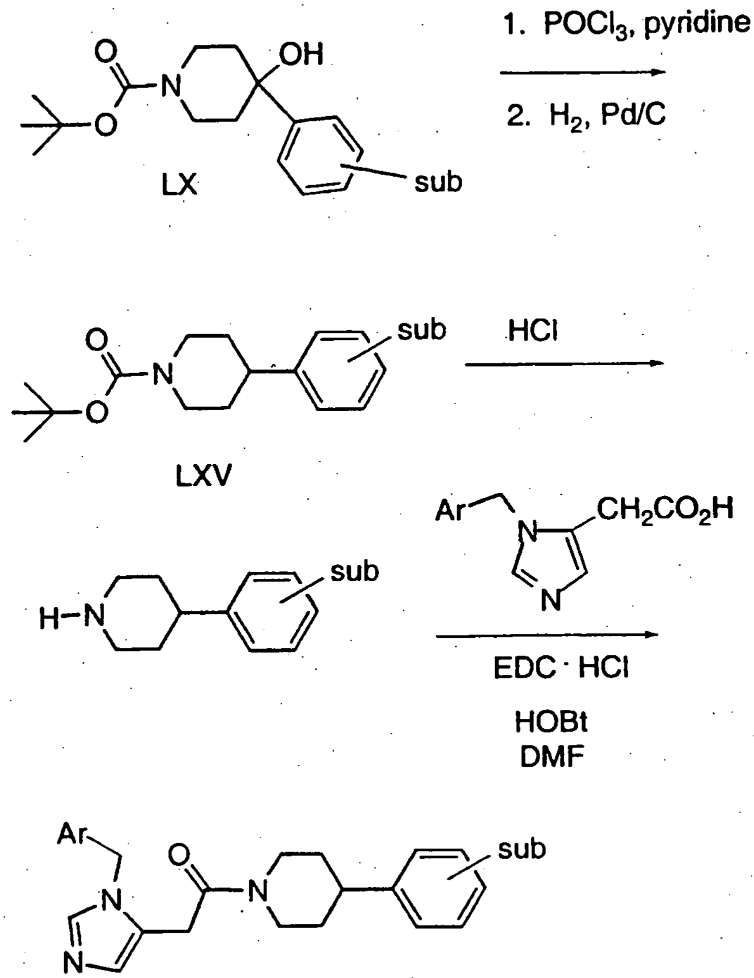


LXIV

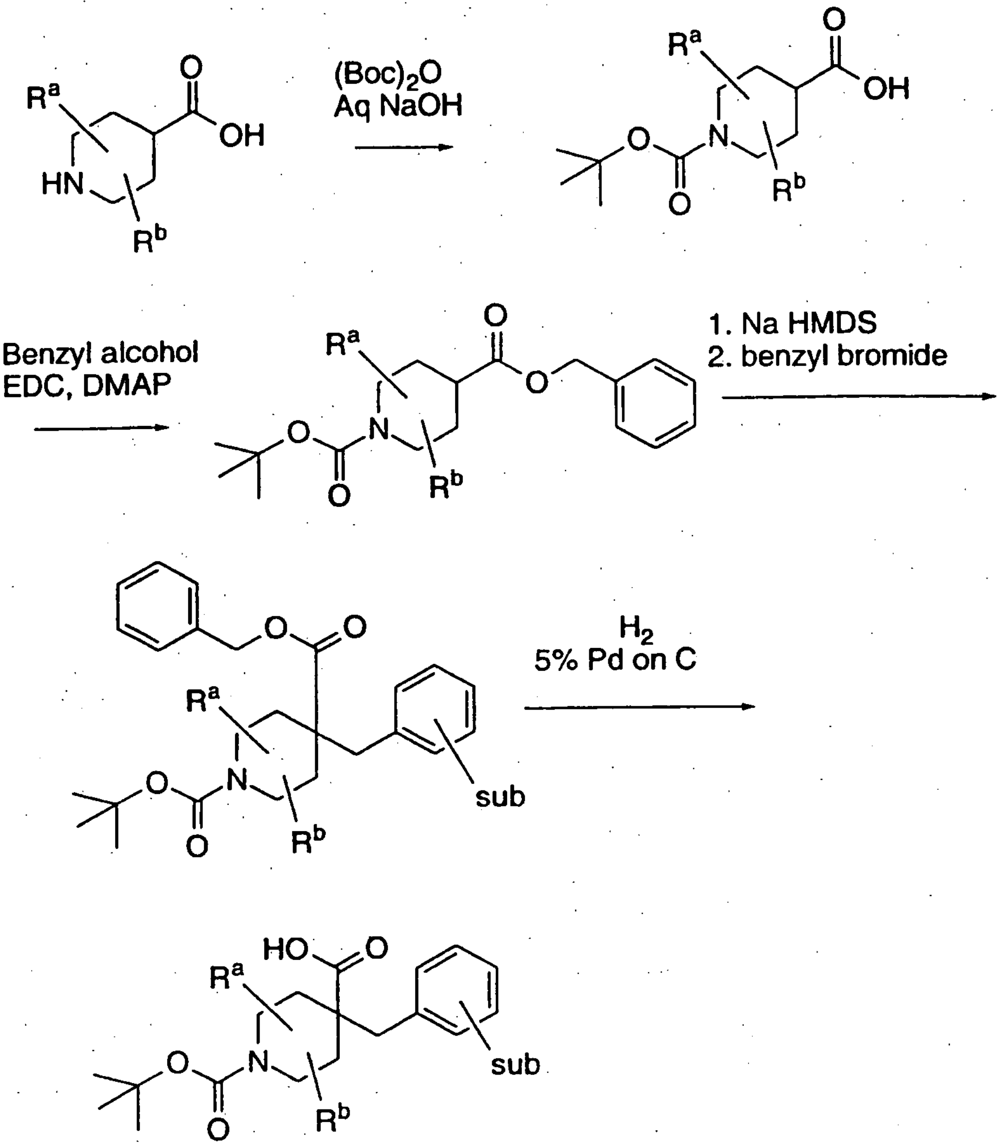
SCHEME 23


OH
sub
HCl
O
N
O
LXIII
OH
sub
H–N
NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
N
N
Tr
OH
sub
(CH2)n+1
N
N
N
Tr

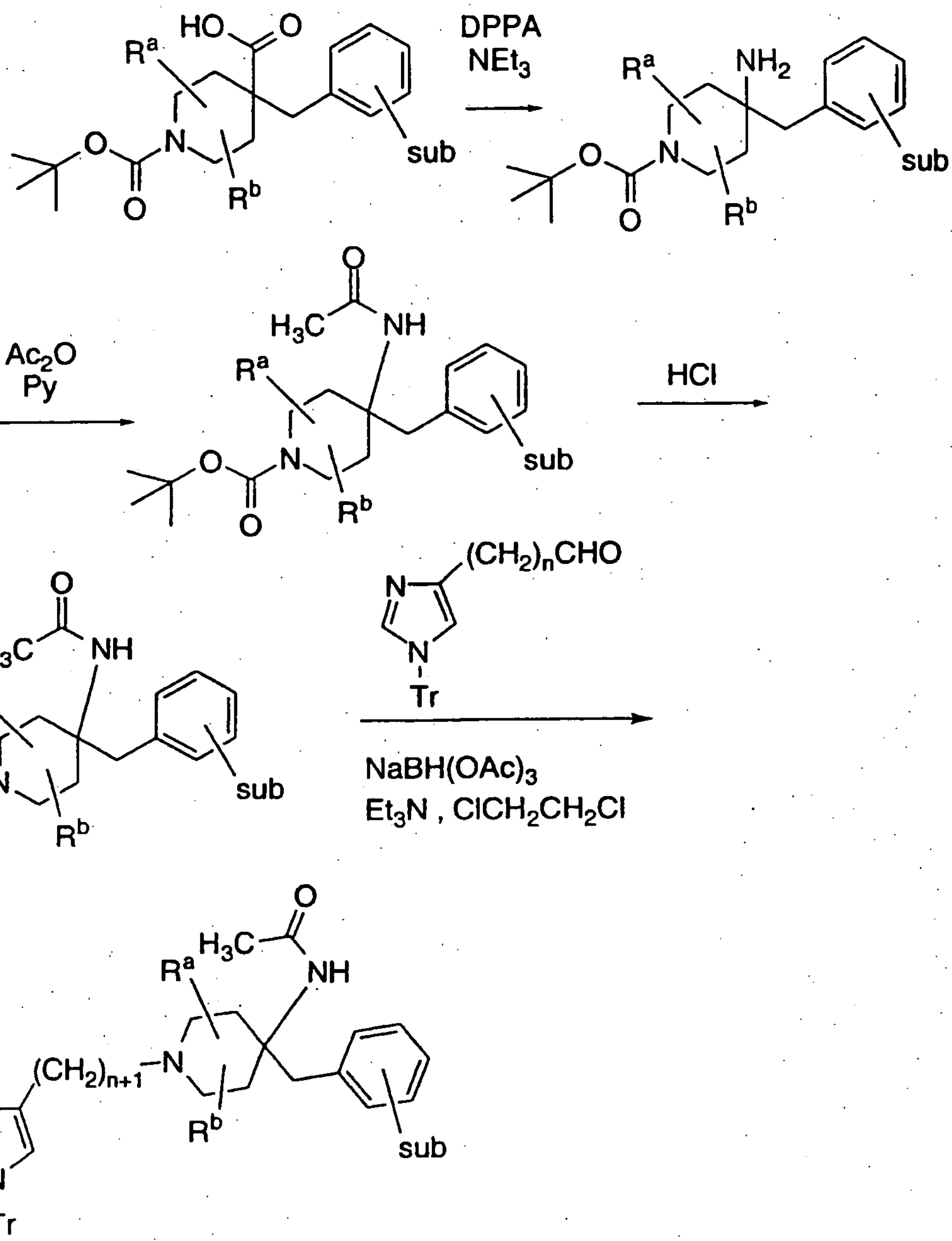
SCHEME 24


1. POCl3, pyridine
2. H2, Pd/C
LX
sub
HCl
LXV
CH2CO2H
Ar
EDC · HCl
HOBt
DMF

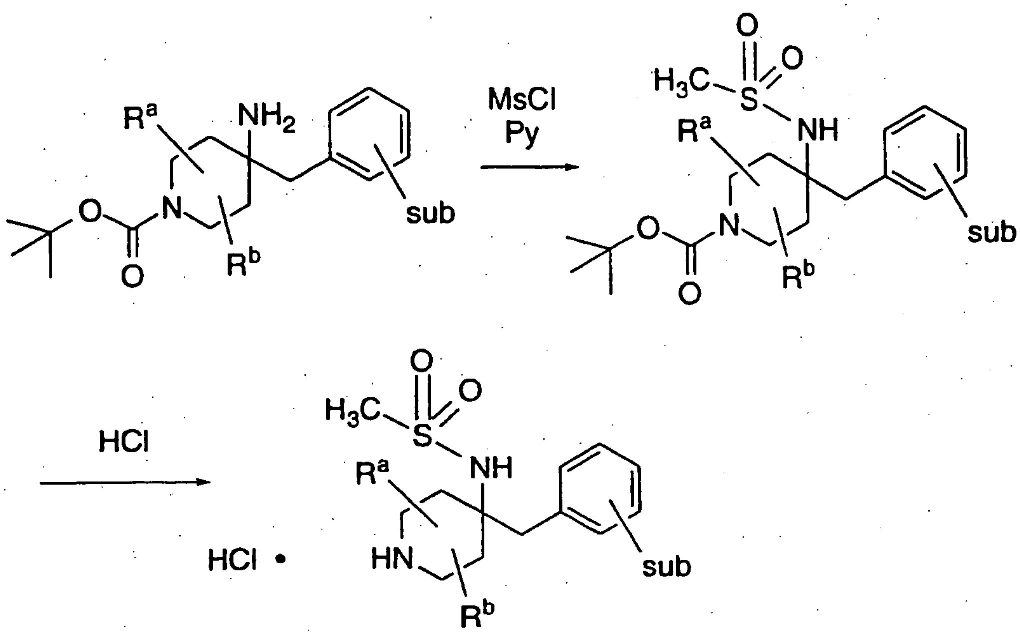
SCHEME 25


(Boc)$_2$O
Aq NaOH
R^a
R^b
HN
OH
O
N
Benzyl alcohol
EDC, DMAP
1. Na HMDS
2. benzyl bromide
H$_2$
5% Pd on C
sub
HO

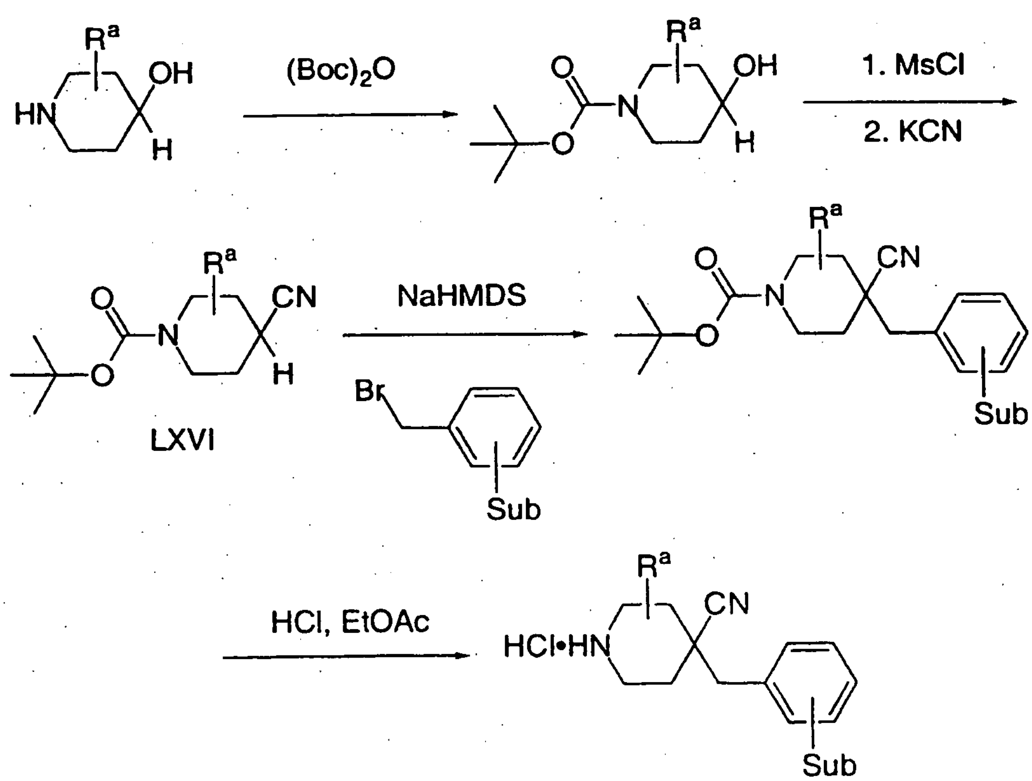
SCHEME 25 (continued)



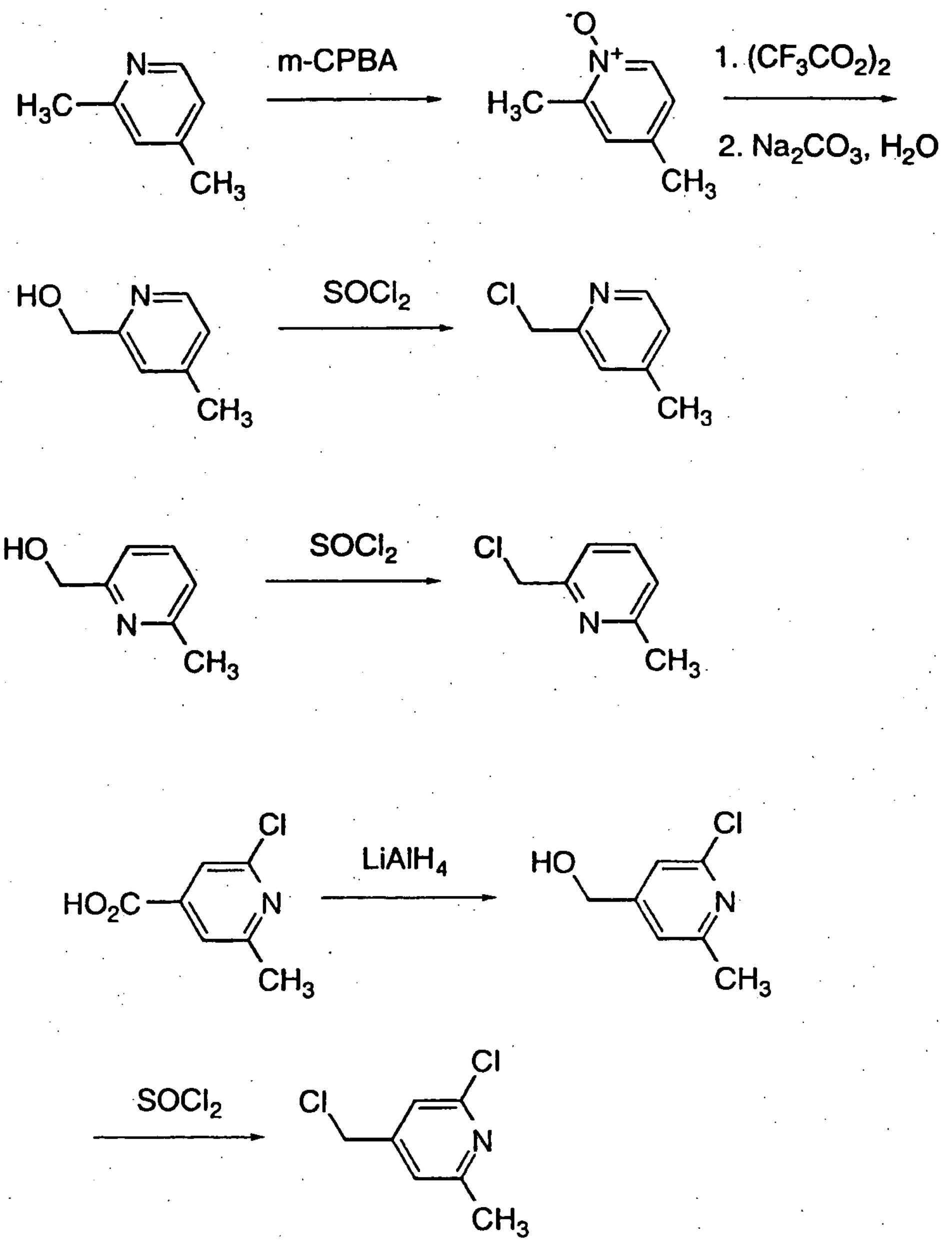
SCHEME 26



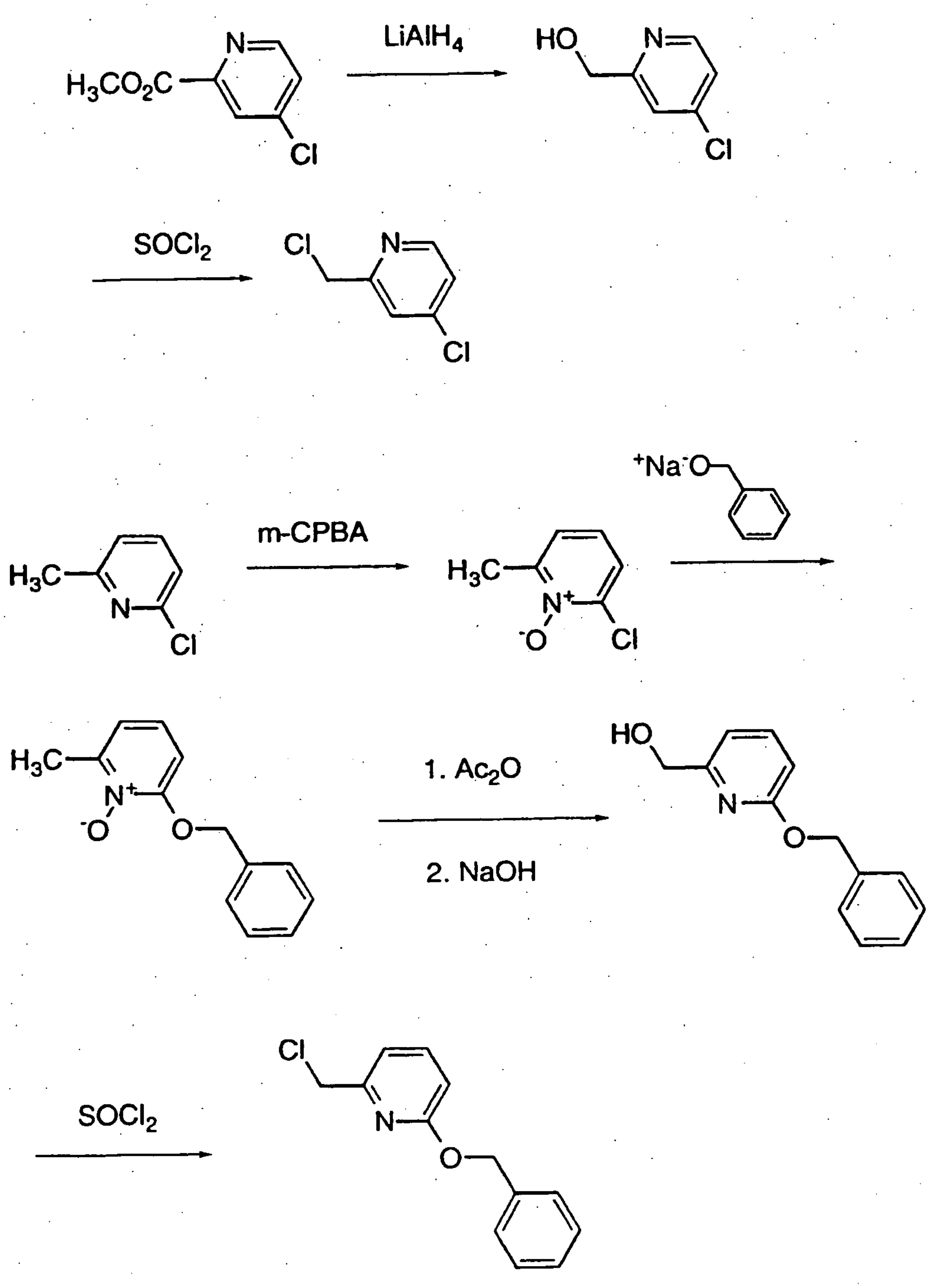
SCHEME 27



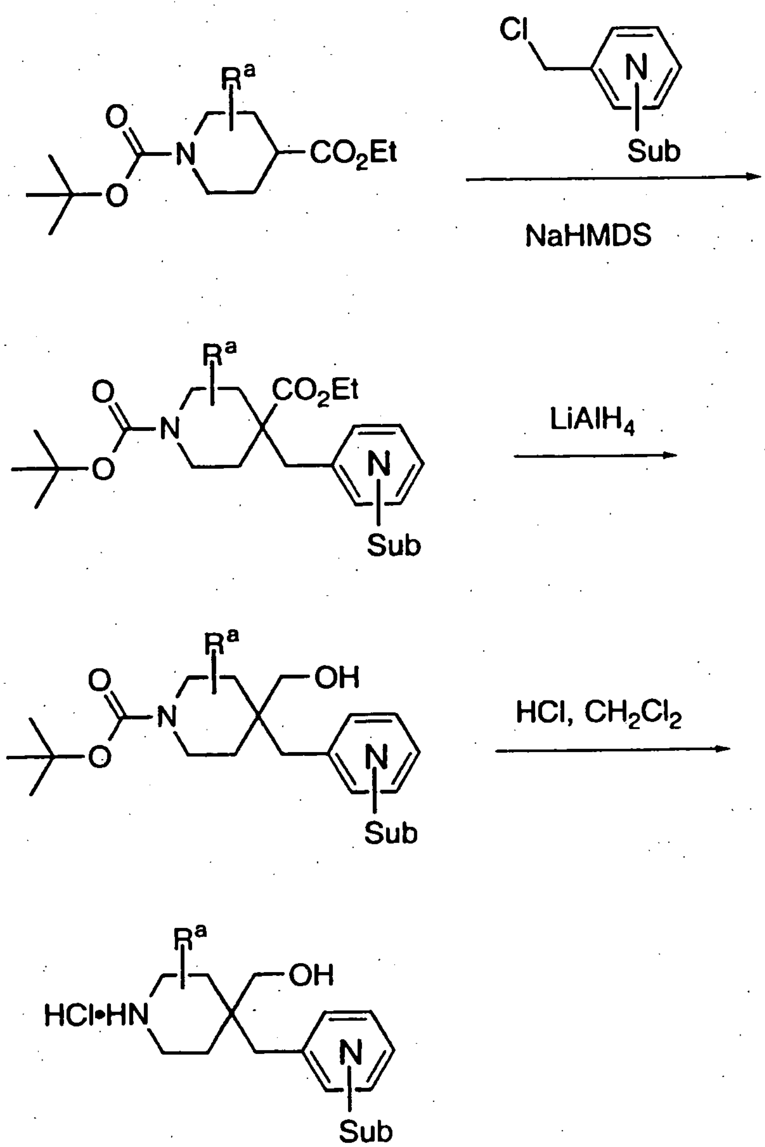
SCHEME 28



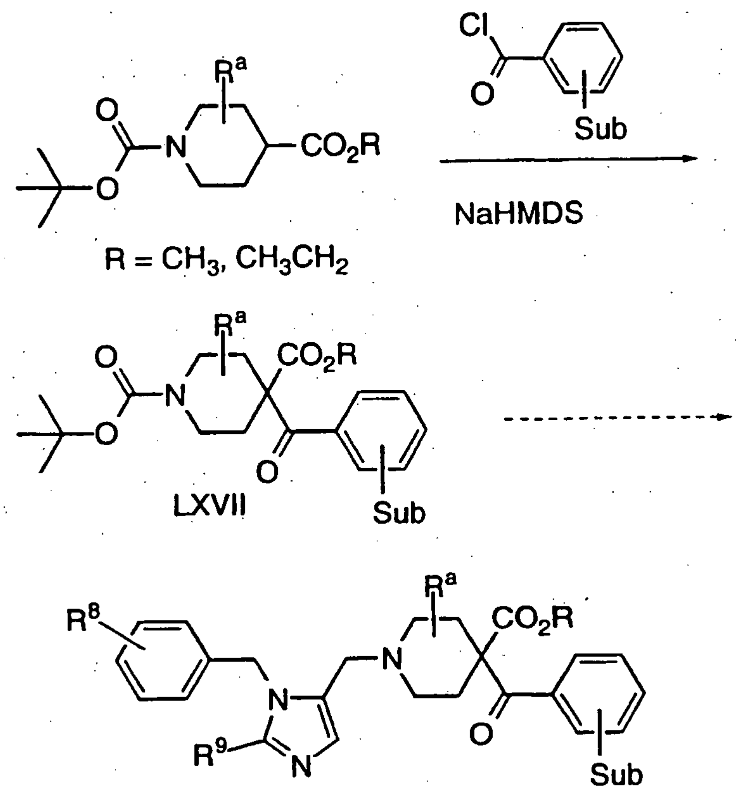
SCHEME 28 (continued)



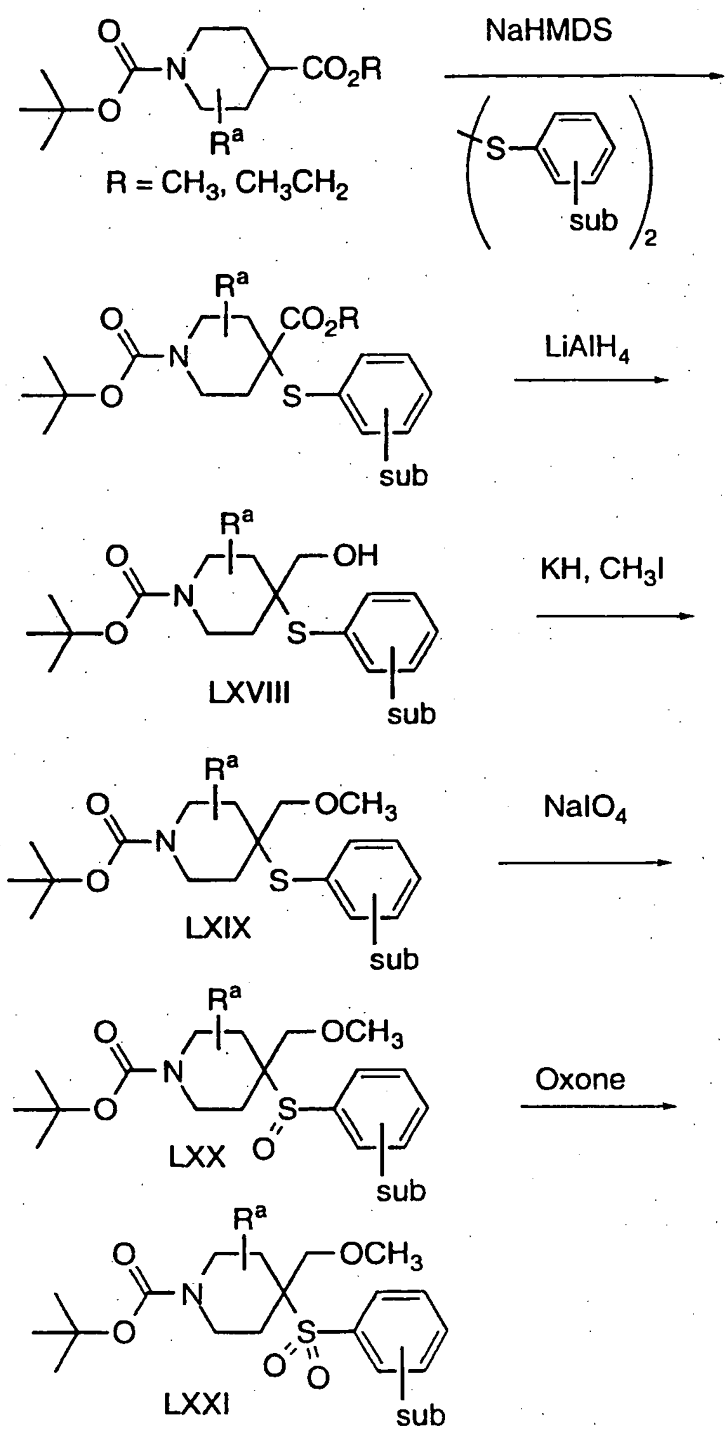
SCHEME 29



SCHEME 30

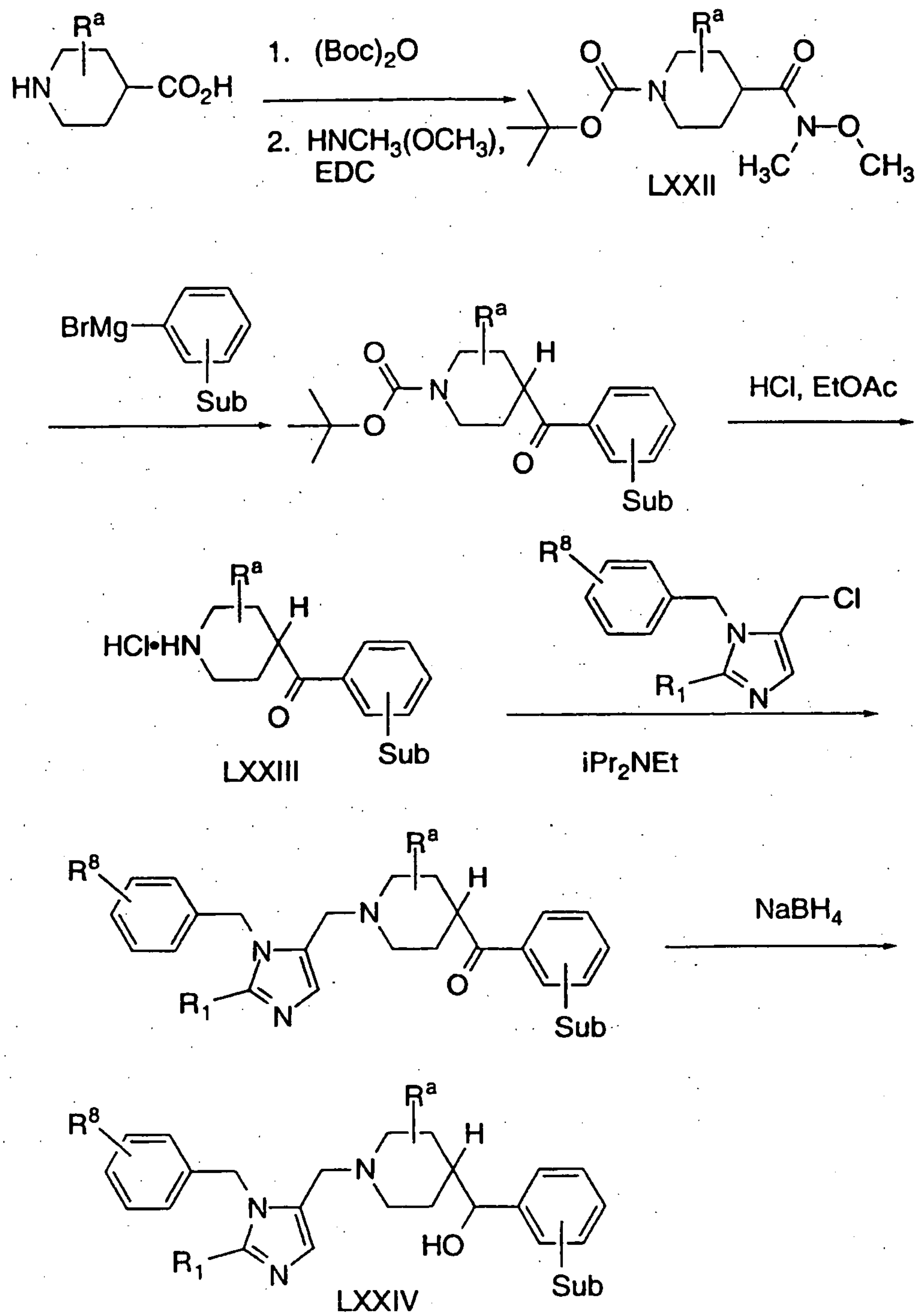


SCHEME 31



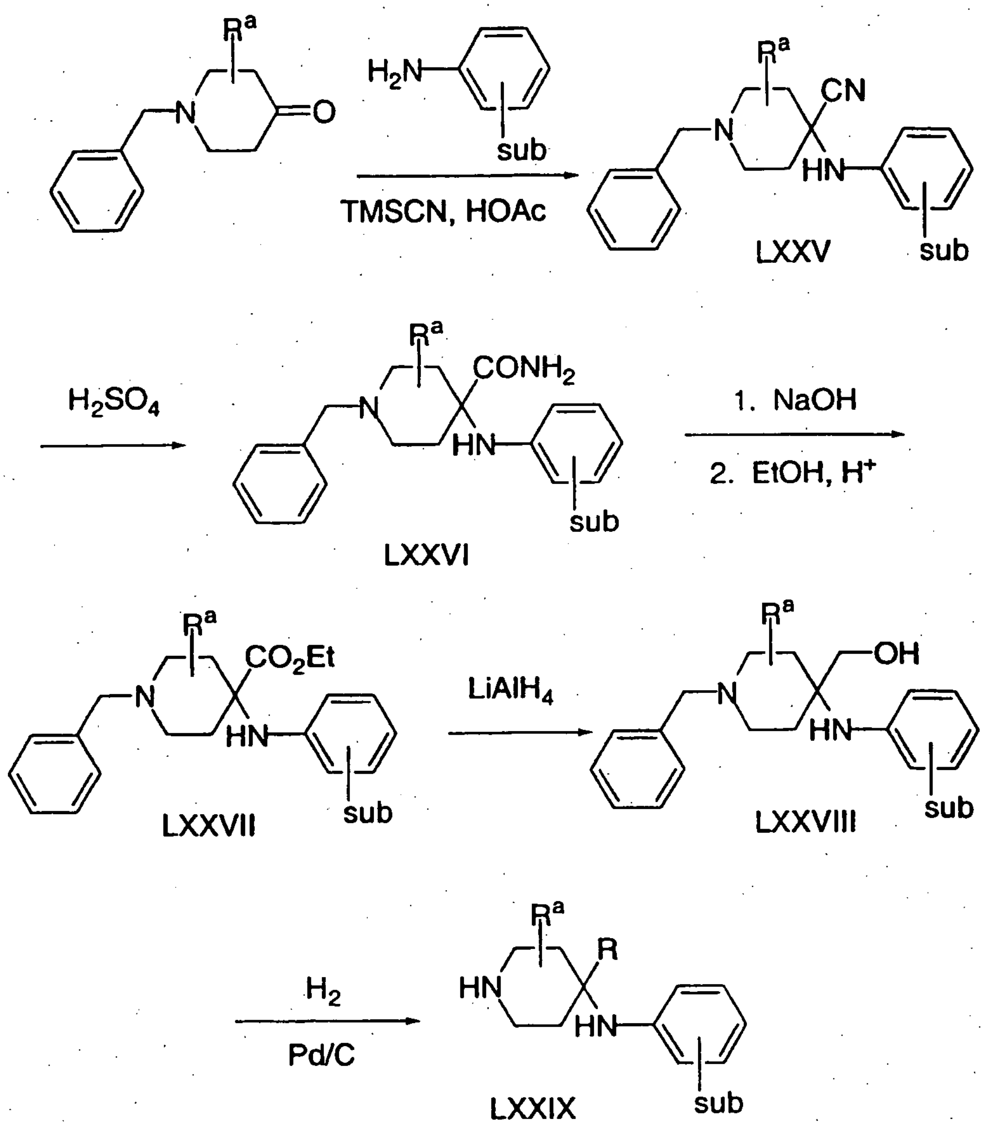
NaHMDS
LiAlH$_4$
KH, CH$_3$I
NaIO$_4$
Oxone
R = CH$_3$, CH$_3$CH$_2$
LXVIII
LXIX
LXX
LXXI

SCHEME 32



R^a
HN
CO_2H
1. $(Boc)_2O$
2. $HNCH_3(OCH_3)$, EDC
O
N
N–O
H_3C
CH_3
LXXII
BrMg
Sub
H
HCl, EtOAc
HCl•HN
LXXIII
R^8
Cl
R_1
iPr_2NEt
$NaBH_4$
HO
LXXIV

SCHEME 33



The compounds of the formula (II) are prepared by employing reactions as shown in the Schemes 34-48, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5; substituent "sub" represents a suitable substituent on the substituent Z. The point

of attachment of such substituents to a ring is illustrative only and is not meant to be limiting. The compounds referred to in the Synopsis of Schemes 34-48 are numbered starting sequentially with 1 and ending with 45.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

Synopsis of Schemes 34-48:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 34-43 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl side chain. Thus, in Scheme 34, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinone **1** may be reacted under coupling conditions with a suitably substituted iodobenzyl alcohol to provide the intermediate alcohol **2**. The intermediate alcohol **2** may converted to the corresponding bromide **3**. The bromide **3** may be coupled to a suitably substituted benzylimidazolyl **4** to provide, after deprotection, the instant compound **5**.

Schemes 35-37 illustrate methods of synthesizing related or analogous key alcohol intermediates, which can then be processed as described in Scheme 34. Thus, Scheme 35 illustrates pyridinonyl-pyridyl alcohol forming reactions starting with the suitably substituted iodonicotinate **6**.

Scheme 36 illustrates preparation of the intermediate alcohol **9** wherein the terminal lactam ring is saturated. Acylation

of a suitably substituted 4-aminobenzyl alcohol **7** with a suitably substituted brominated acyl chloride provides the bisacylated intermediate **8**. Closure of the lactam ring followed by saponifiaction of the remaining acyl group provides the intermediate alcohol. Preparation of the homologous saturated lactam **10** is illustrated in Scheme 37.

Scheme 38 illustrates the synthesis of the alcohol intermediate **13** which incorporates a terminal pyrazinone moiety. Thus, the amide of a suitably substituted amino acid **11** is formed and reacted with glyoxal to form the pyrazine **12**, which then undergoes the Ullmann coupling to form intermediate **13**.

Scheme 39 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **14** may be selectively iodinated to provide the 5-iodoimidazole **15**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **16**. Intermediate **16** can then undergo the alkylation reactions that were described hereinabove.

Scheme 40 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the bicyclic moiety via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **17**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **18**. The amine **18** may then react under conditions well known in the art with various activated bicyclic moieties to provide the instant compounds shown.

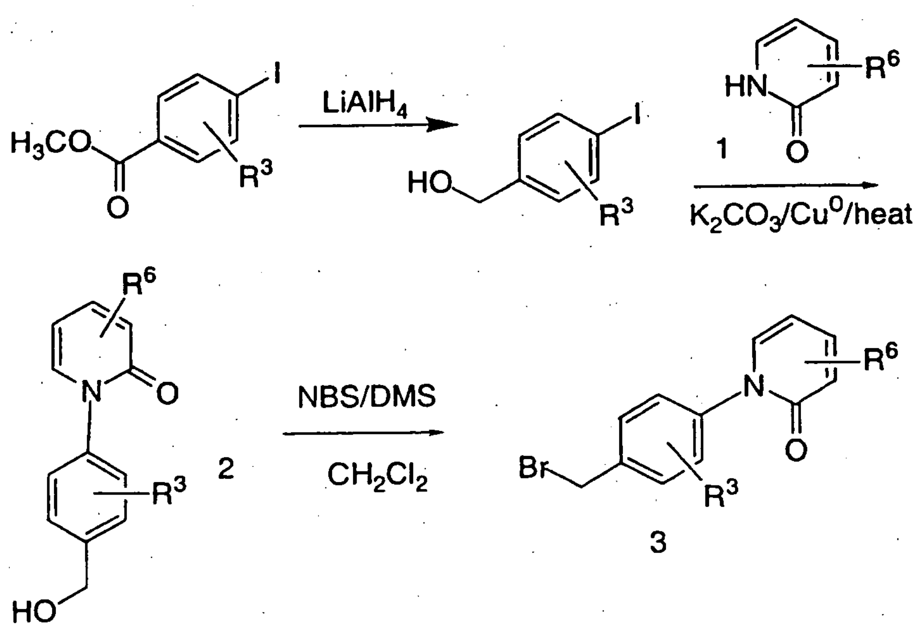
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 41. The suitably substituted phenol **19** may be reacted with methyl N-(cyano)methanimidate to provide the 4-phenoxyimidazole **20**. After selective protection of one of the imidazolyl nitrogens, the intermediate **21** can undergo alkylation reactions as described

for the benzylimidazoles hereinabove.

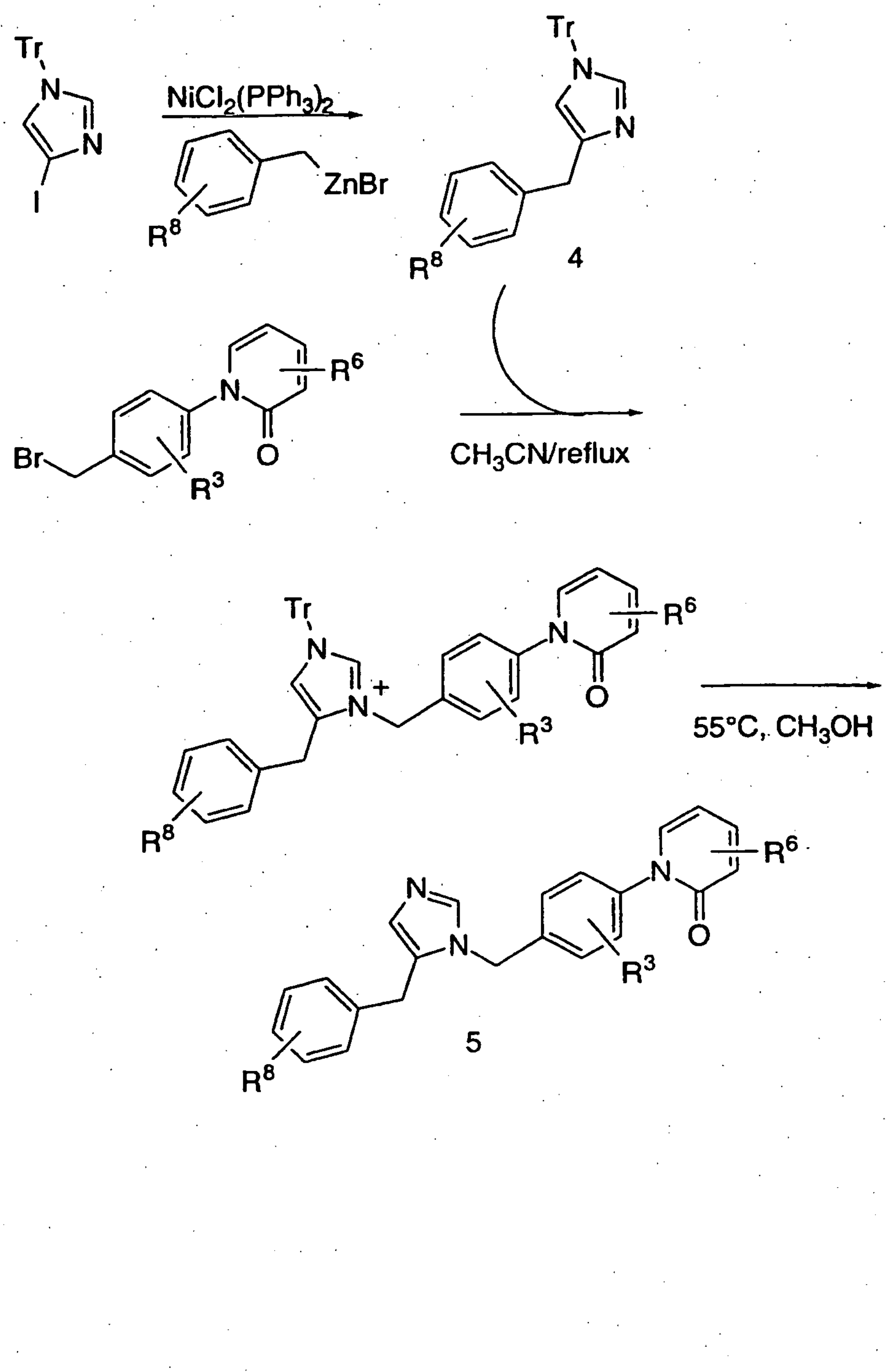
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 42. Thus, the N-protected imidazolyl iodide **22** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **23**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 34) provides the instant compound **24**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 43 illustrates incorporation of an acetyl moiety as the $(CR^2{}_2)_pX(CR^2{}_2)_p$ linker of the instant compounds. Thus the readily available methylphenone **25** undergoes the Ullmann reaction and the acetyl is brominated to provide intermediate **26**. Reaction with the imidazolyl reagent **4** provides, after deprotection, the instant compound **27**.

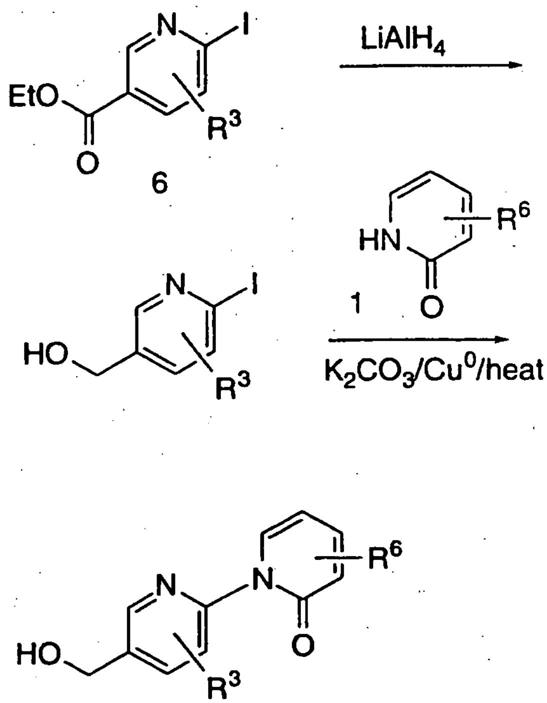
SCHEME 34



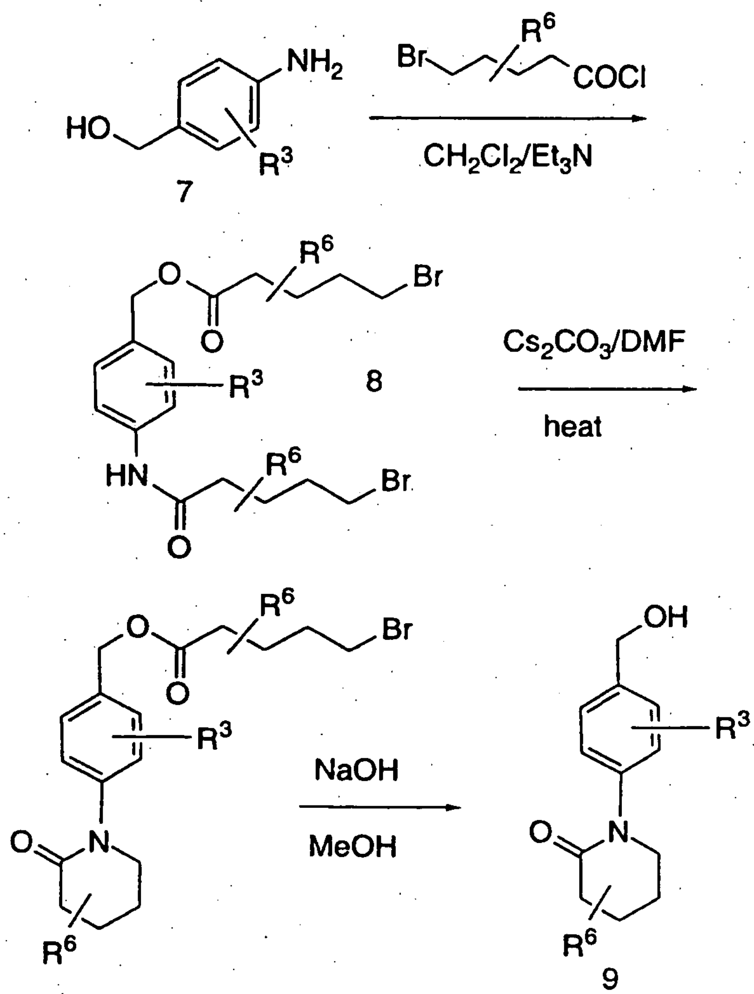
SCHEME 34 (continued)



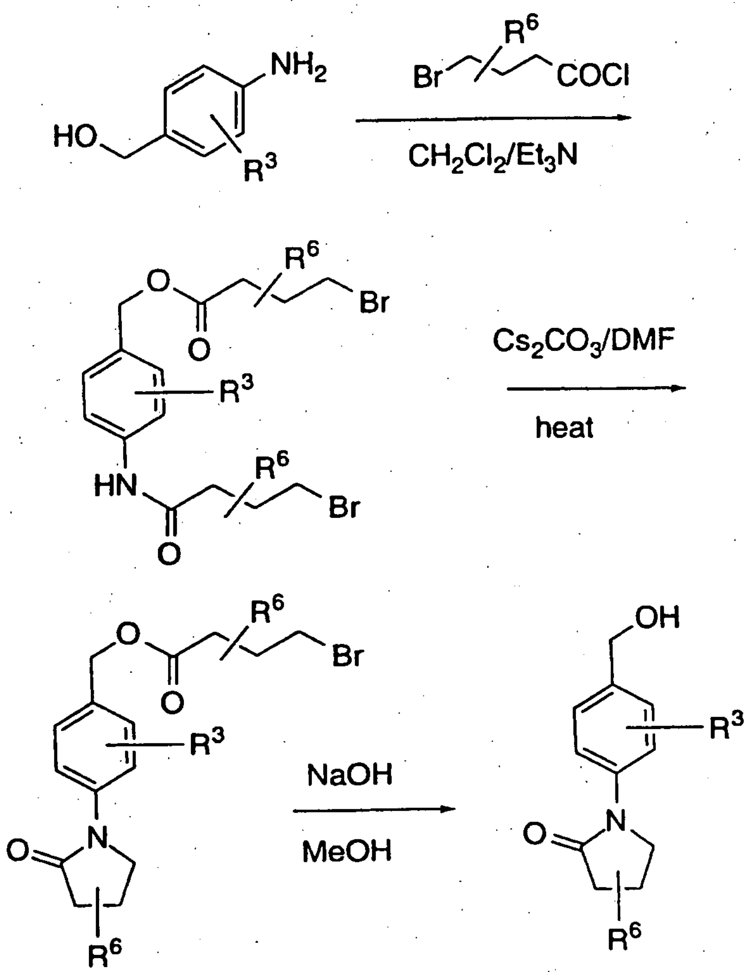
SCHEME 35



SCHEME 36



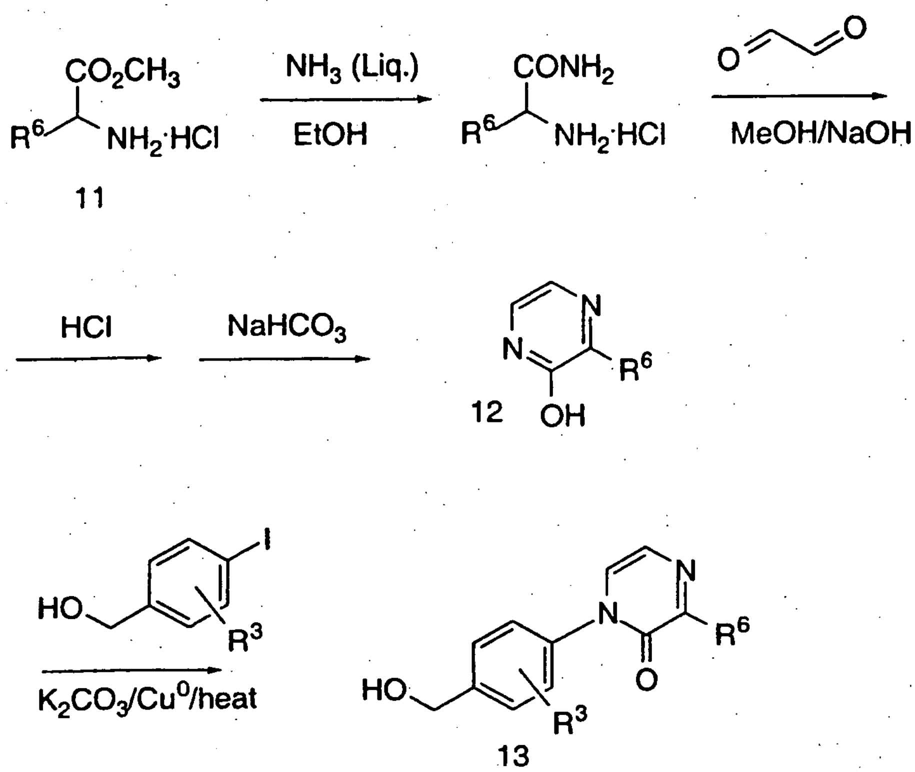
SCHEME 37



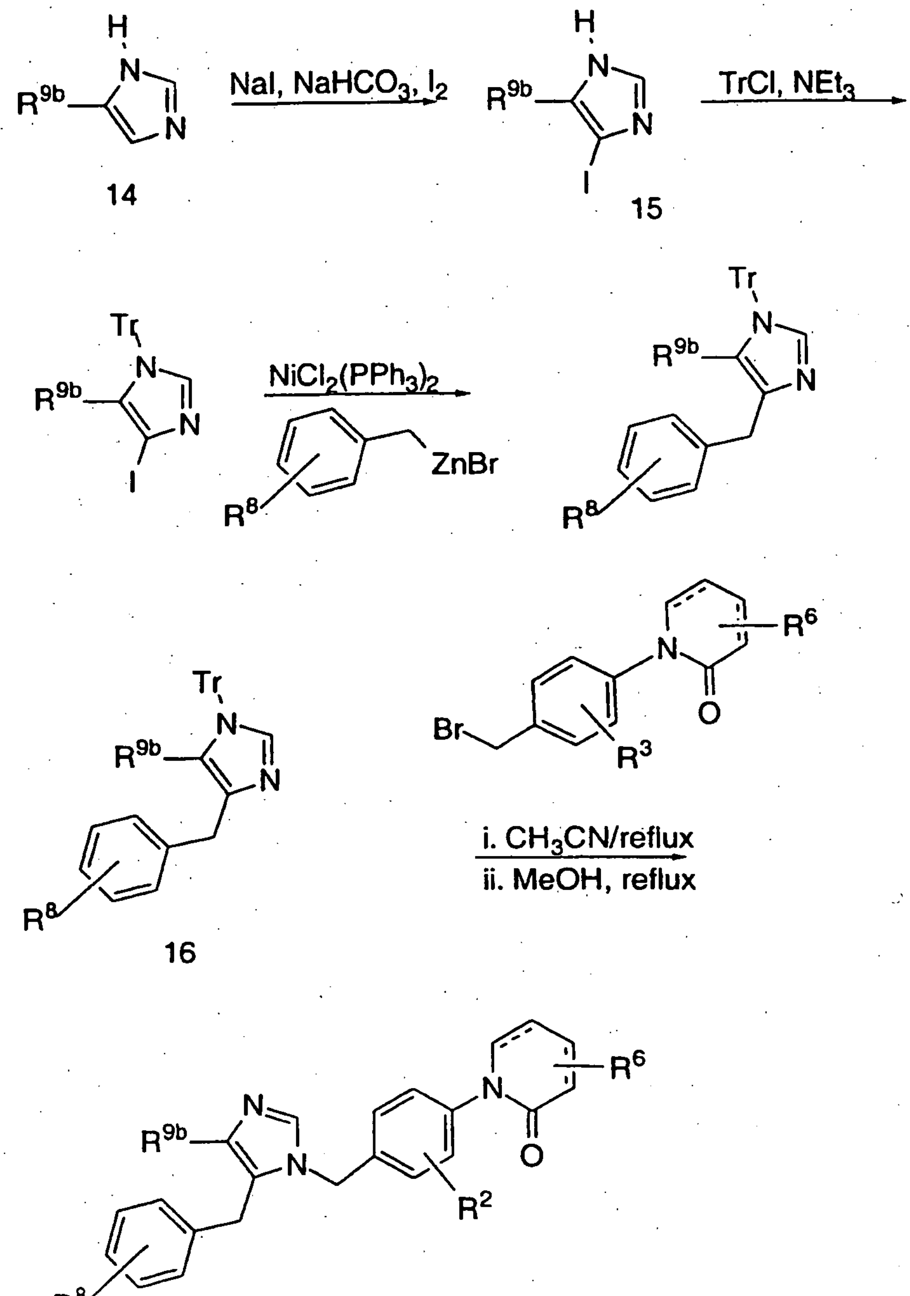
NH2
HO
R3
Br
R6
COCl
CH2Cl2/Et3N
O
Br
Cs2CO3/DMF
heat
HN
N
OH
NaOH
MeOH

10

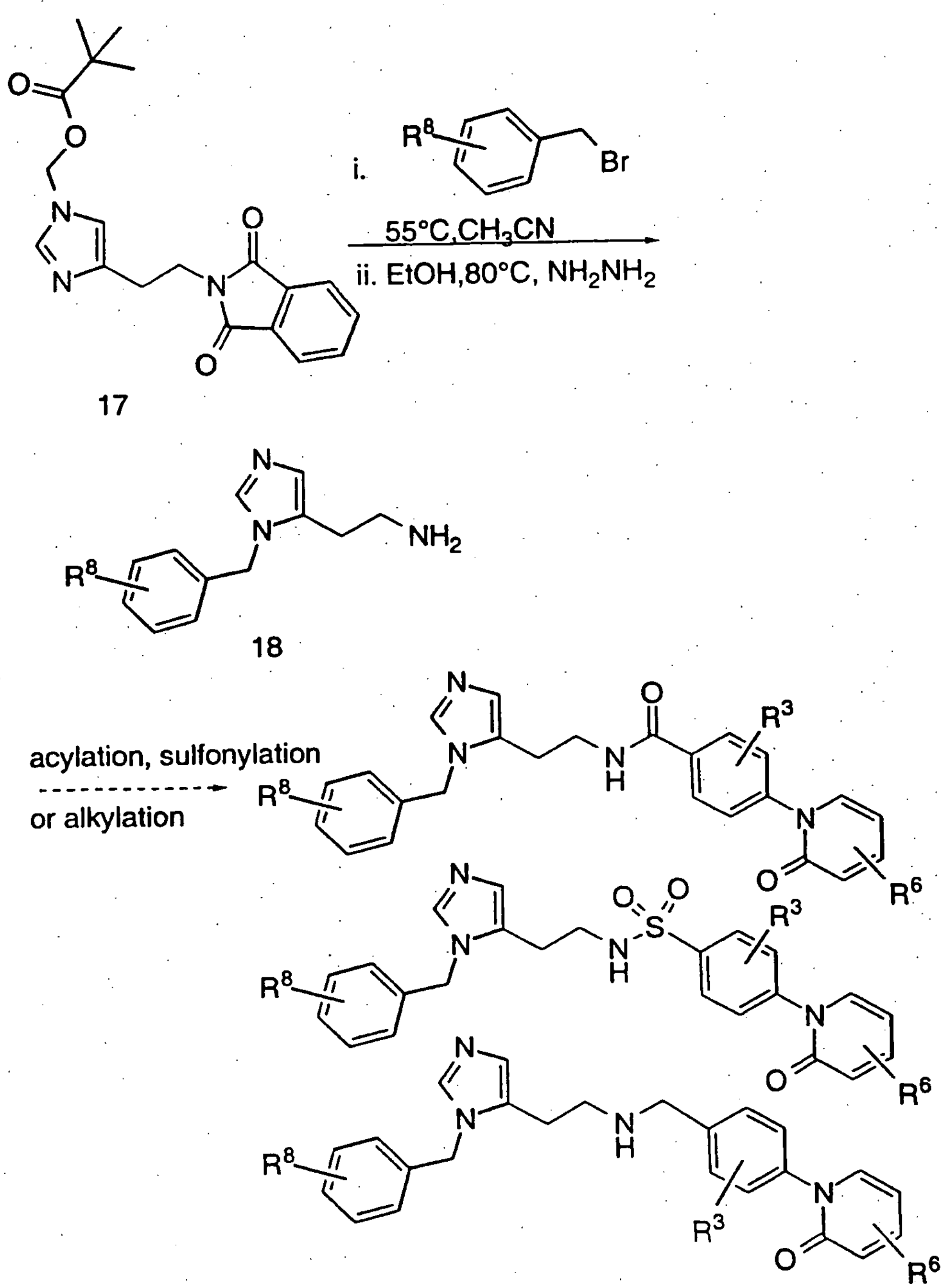
SCHEME 38


CO2CH3
R6
NH2·HCl
11
NH3 (Liq.)
EtOH
CONH2
R6
NH2·HCl
MeOH/NaOH
HCl
NaHCO3
N
N
R6
12
OH
I
HO
R3
K2CO3/Cu0/heat
N
N
R6
O
HO
R3
13

SCHEME 39

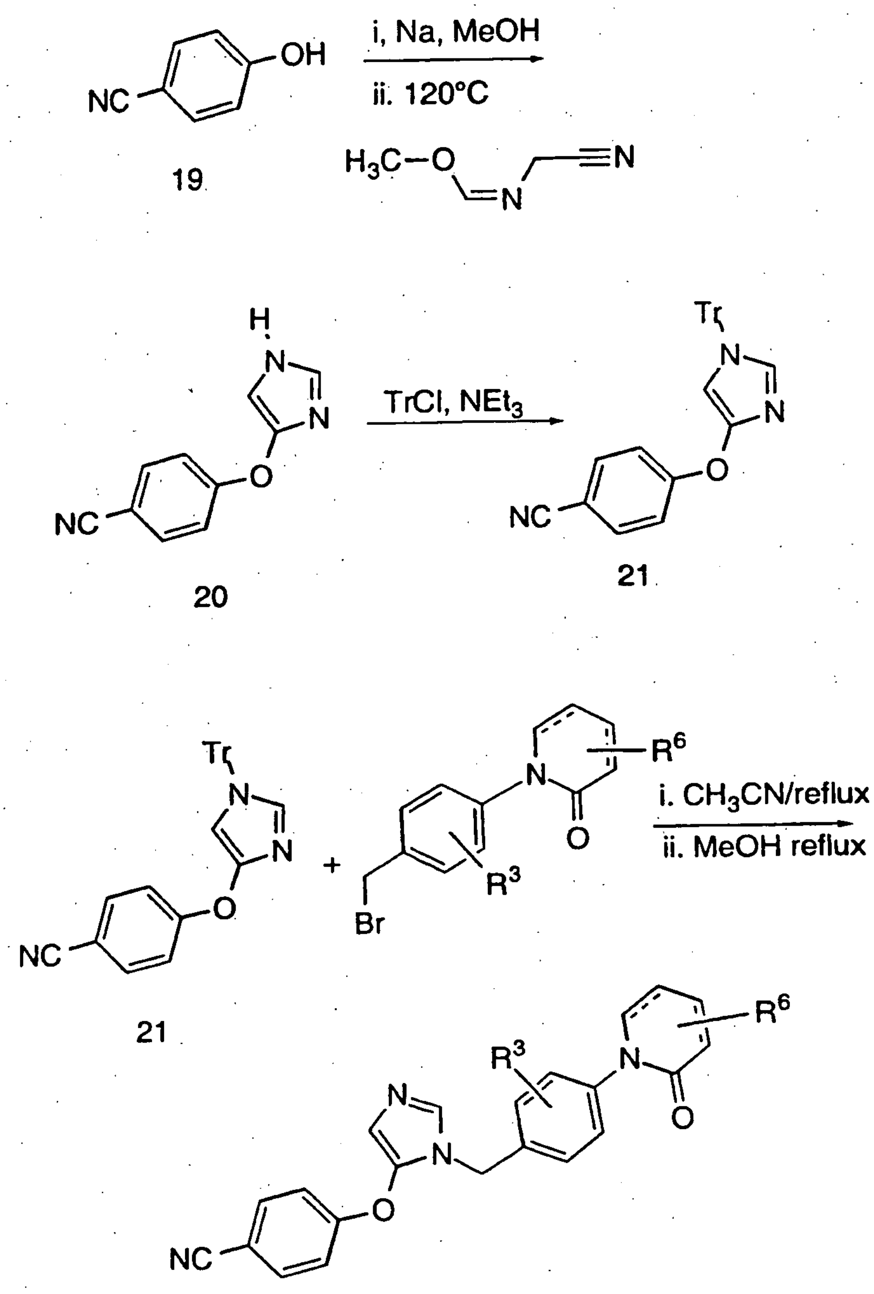

H
R^9b
N
N
NaI, NaHCO3, I2
H
R^9b
N
N
I
TrCl, NEt3
14
15
Tr
R^9b
N
N
I
NiCl2(PPh3)2
ZnBr
R^8
Tr
R^9b
N
N
R^8
Tr
R^9b
N
N
R^8
16
Br
N
O
R^6
R^3
i. CH3CN/reflux
ii. MeOH, reflux
R^9b
N
N
R^8
N
O
R^6
R^2

SCHEME 40

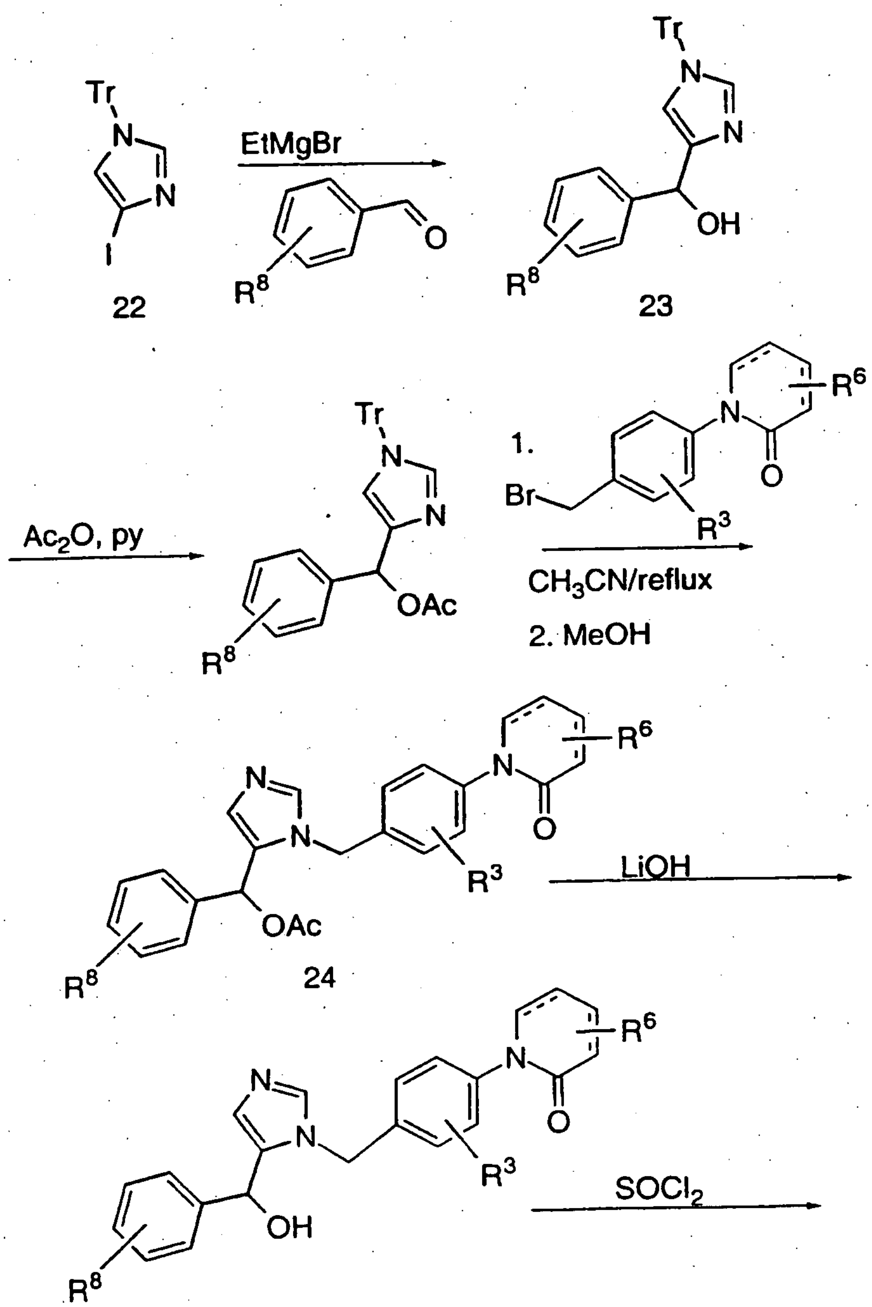


i.
R8
Br
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
17
18
NH2
acylation, sulfonylation
or alkylation
R3
R6

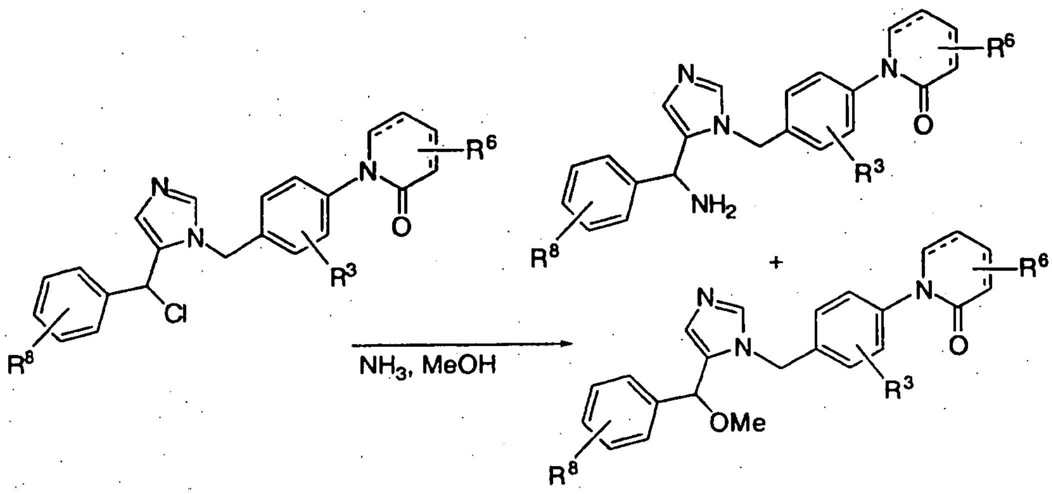
SCHEME 41


NC
OH
i, Na, MeOH
ii. 120°C
19
H₃C–O
N
N
H
N
N
O
NC
TrCl, NEt₃
Tr
N
N
O
NC
20
21
Tr
N
N
O
NC
21
+
Br
R³
N
O
R⁶
i. CH₃CN/reflux
ii. MeOH reflux
R³
N
N
O
NC
N
O
R⁶

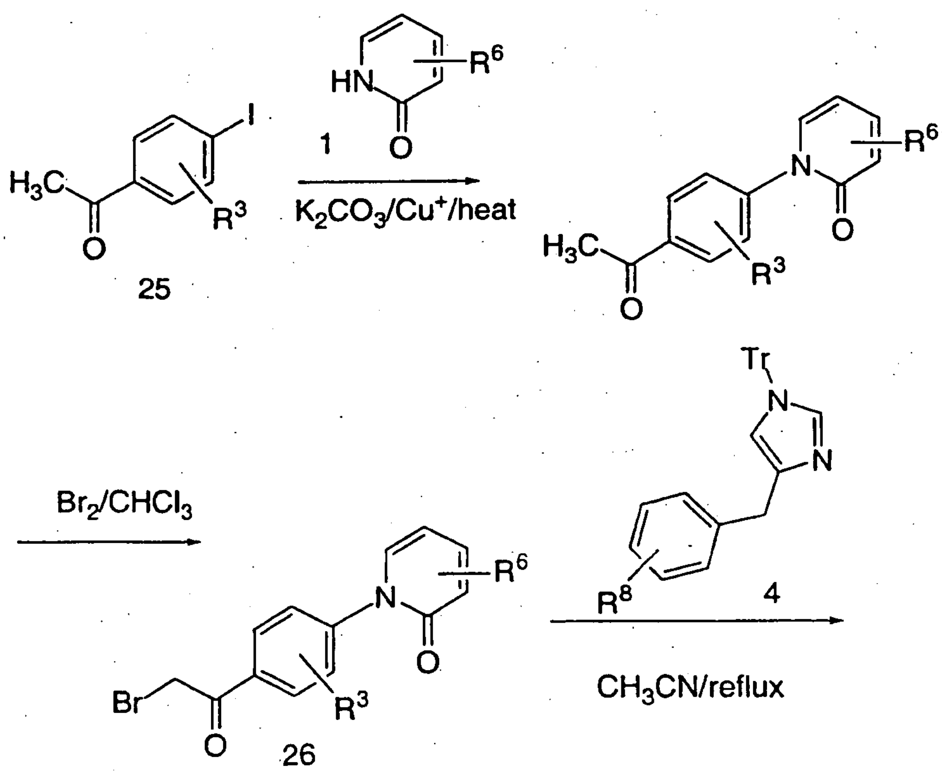
SCHEME 42


Tr
N
N
I
EtMgBr
O
R8
22
Tr
N
N
OH
R8
23
Ac2O, py
Tr
N
N
OAc
R8
1.
Br
N
O
R6
R3
CH3CN/reflux
2. MeOH
N
N
OAc
R8
N
O
R6
R3
24
LiOH
N
N
OH
R8
N
O
R6
R3
SOCl2

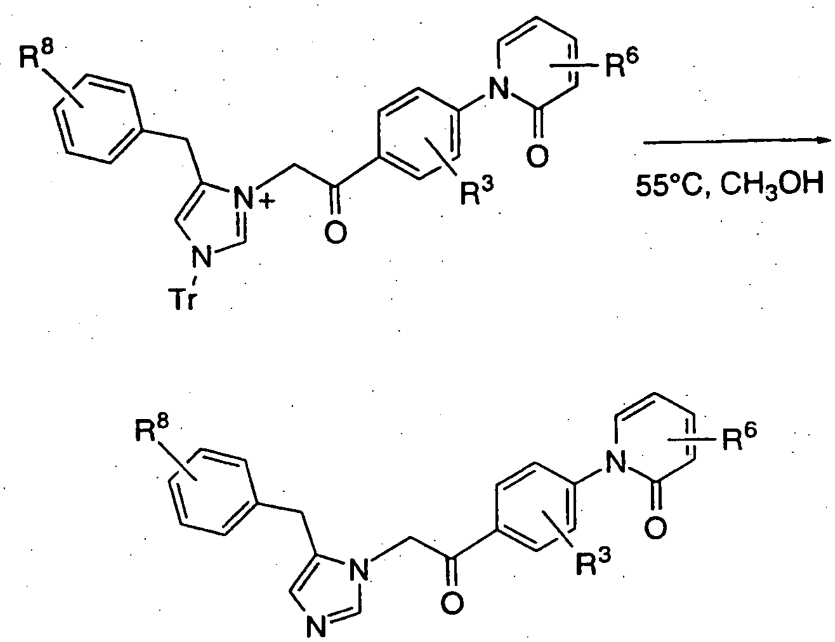
SCHEME 42 (continued)



SCHEME 43



SCHEME 43 (continued)



27

Schemes 44-48 illustrate reactions wherein the moiety

$$\overset{(R^8)_r}{\overset{|}{V}} - A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n\left(\overset{(R^9)_q}{\overset{|}{W}}\right)_t - (CR^1{}_2)_p\text{-}X$$

incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in Schemes hereinabove and other arylheteroaryl intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid. Knochel chemistry may be utilized, as

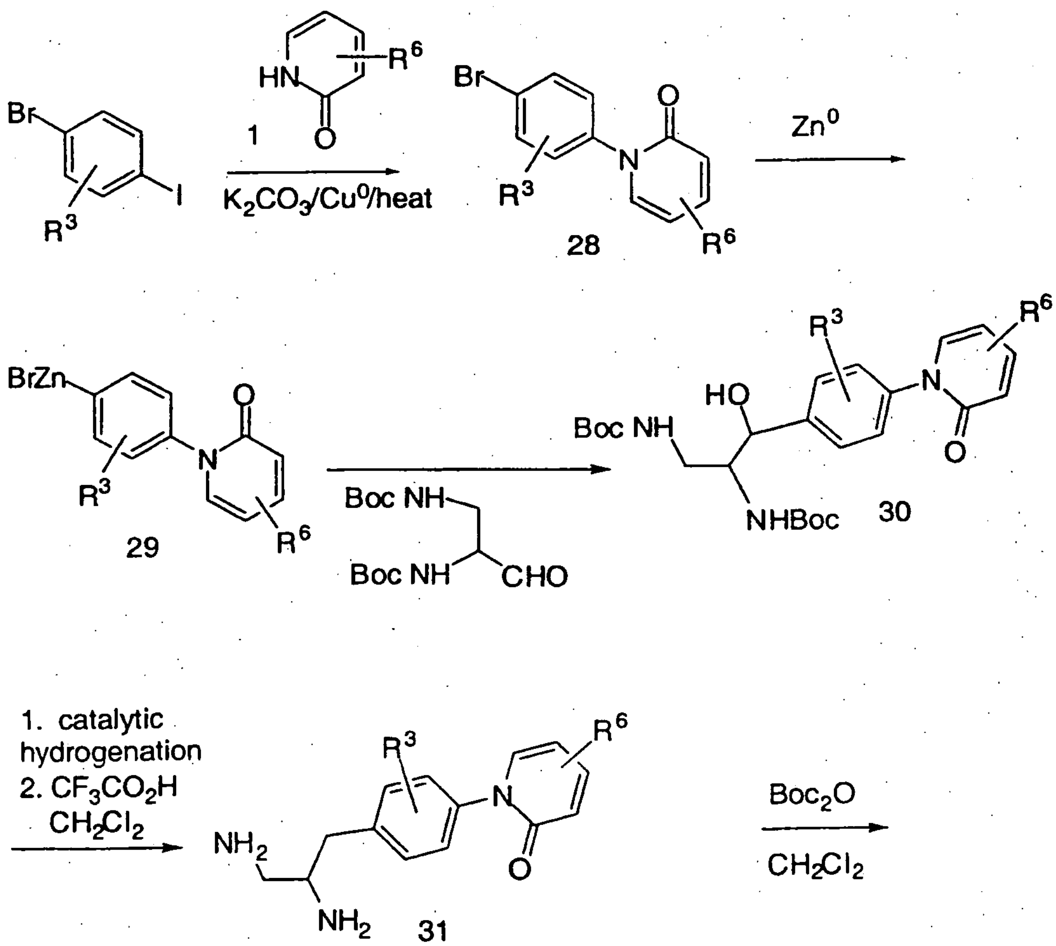
shown in Scheme 44, to incorporate the arylpyridinone moiety. Thus, a suitably substituted 4-(bromo)iodobenzene is coupled to a suitably substituted pyridinone 1 as previously described above. The resulting bromide **28** is treated with zinc(0) and the zinc bromide reagent **29** is reacted with an aldehyde to provide the C-alkylated instant compound **30**. Compound **30** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoroacetic acid in methylene chloride to give the final compound **31**. The compound **31** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **31** can further be selectively protected to obtain **32**, which can subsequently be reductively alkylated with a second aldehyde to obtain **33**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **34** can be accomplished by literature procedures.

If the arylpyridinone zinc bromide reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **35** in Scheme 45, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 45, 46). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as alkyl lithium reagents, to obtain secondary alcohols such as **37**. In addition, the fully deprotected amino alcohol **38** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **39** (Scheme 46), or tertiary amines.

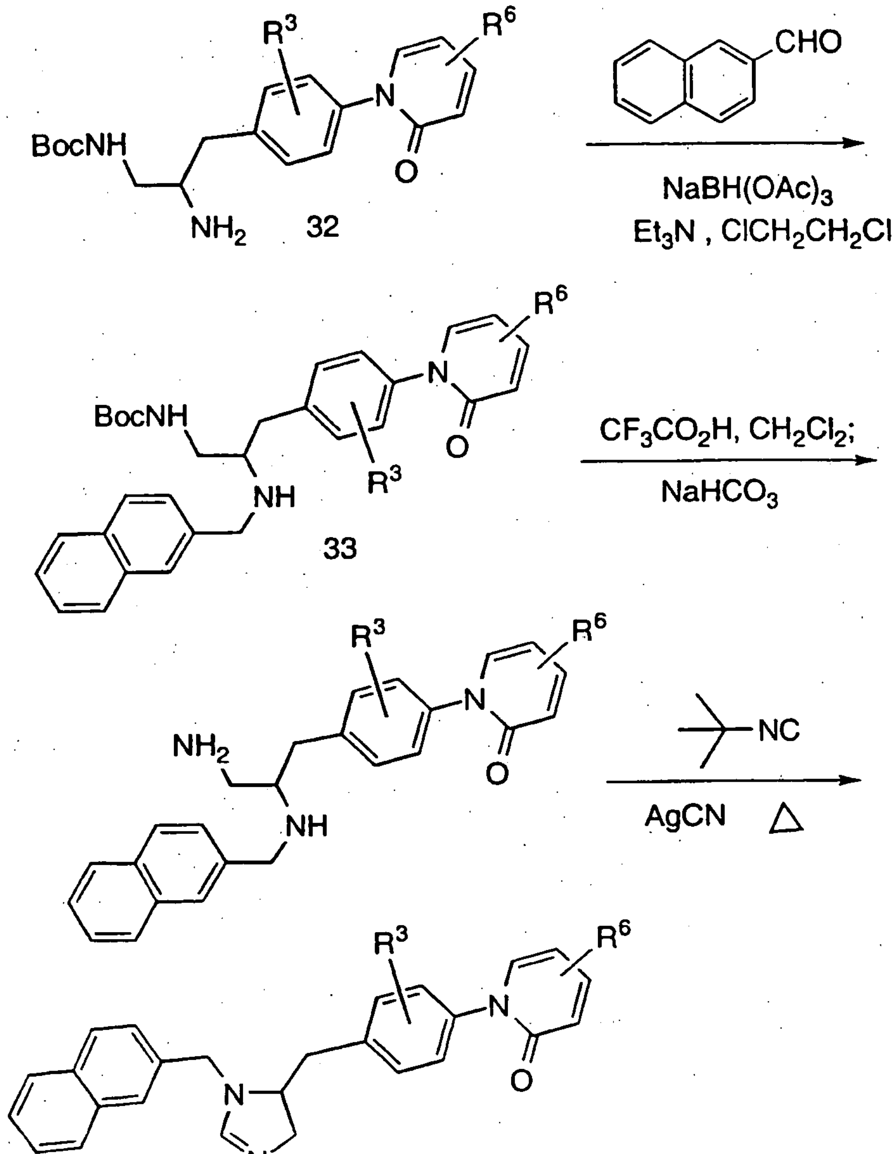
The Boc protected amino alcohol **36** can also be utilized to synthesize 2-aziridinylmethylarylpyridinone such as **40** (Scheme 47). Treating **36** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **40**. The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **41**.

In addition, the arylpyridinone subunit reagent can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **43**, as shown in Scheme 48. When R' is an aryl group, **43** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **44**. Alternatively, the amine protecting group in **43** can be removed, and O-alkylated phenolic amines such as **45** produced.

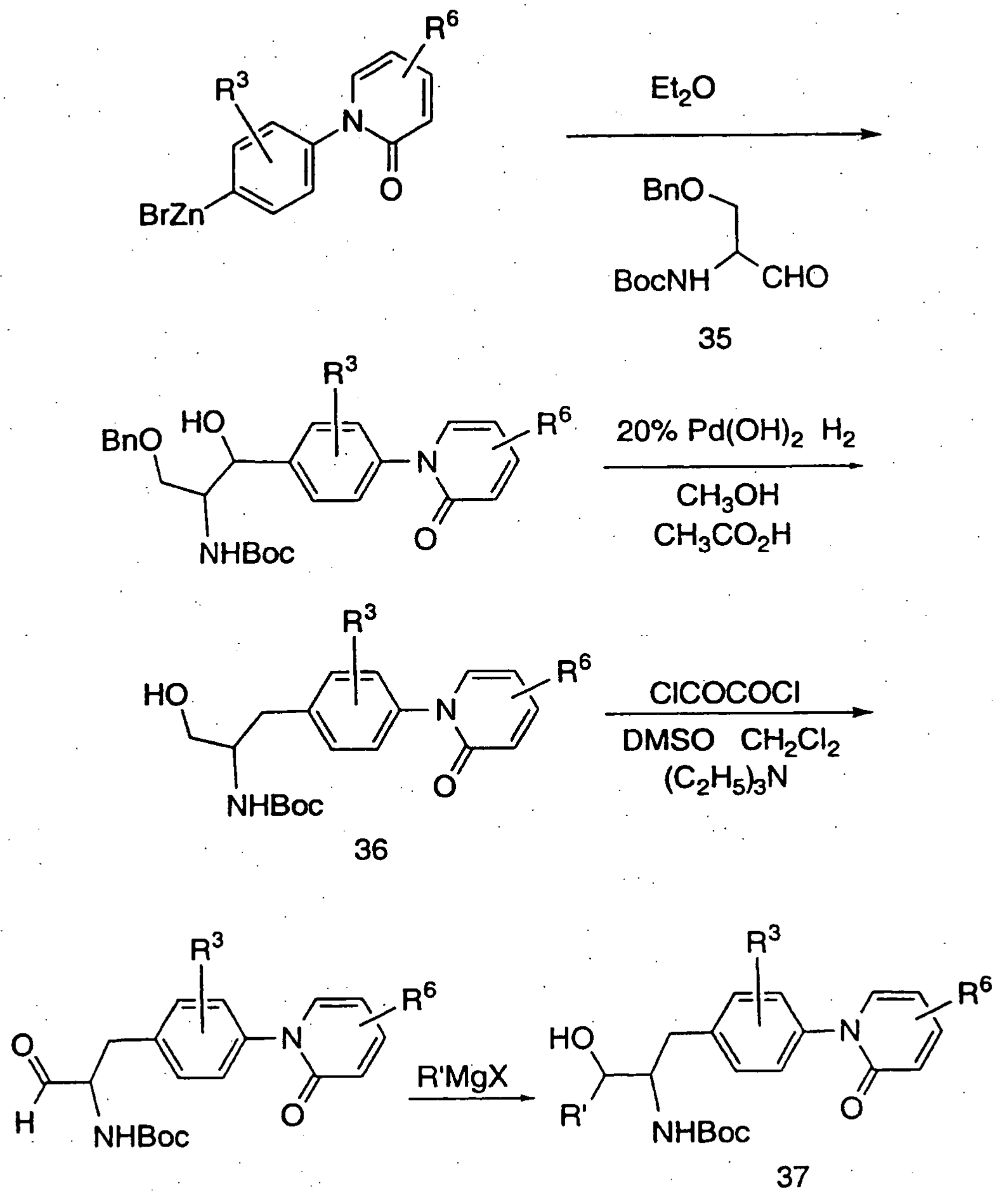
SCHEME 44



SCHEME 44 (continued)

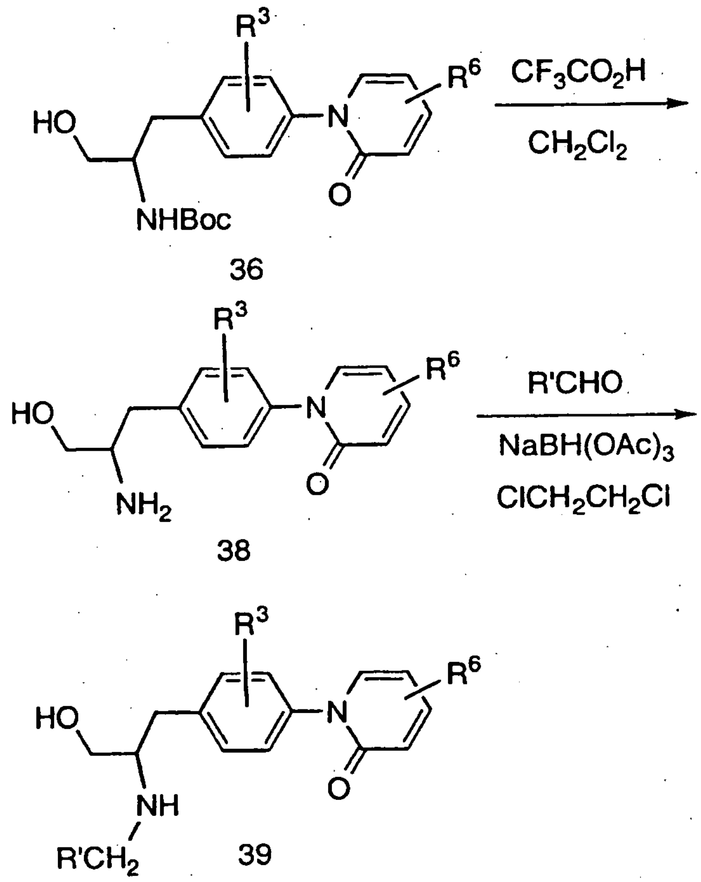


SCHEME 45

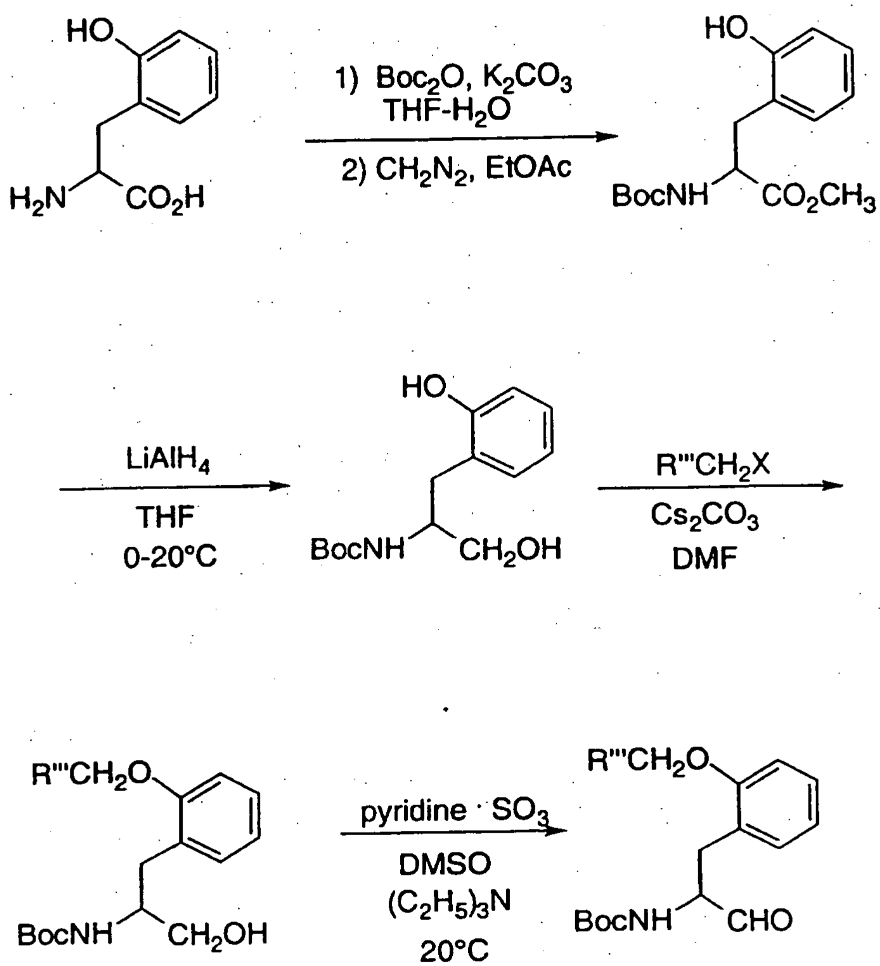

R3
R6
BrZn
N
O
Et2O
BnO
BocNH
CHO
35
HO
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
36
ClCOCOCl
DMSO CH2Cl2
(C2H5)3N
H
R'MgX
R'
37

5

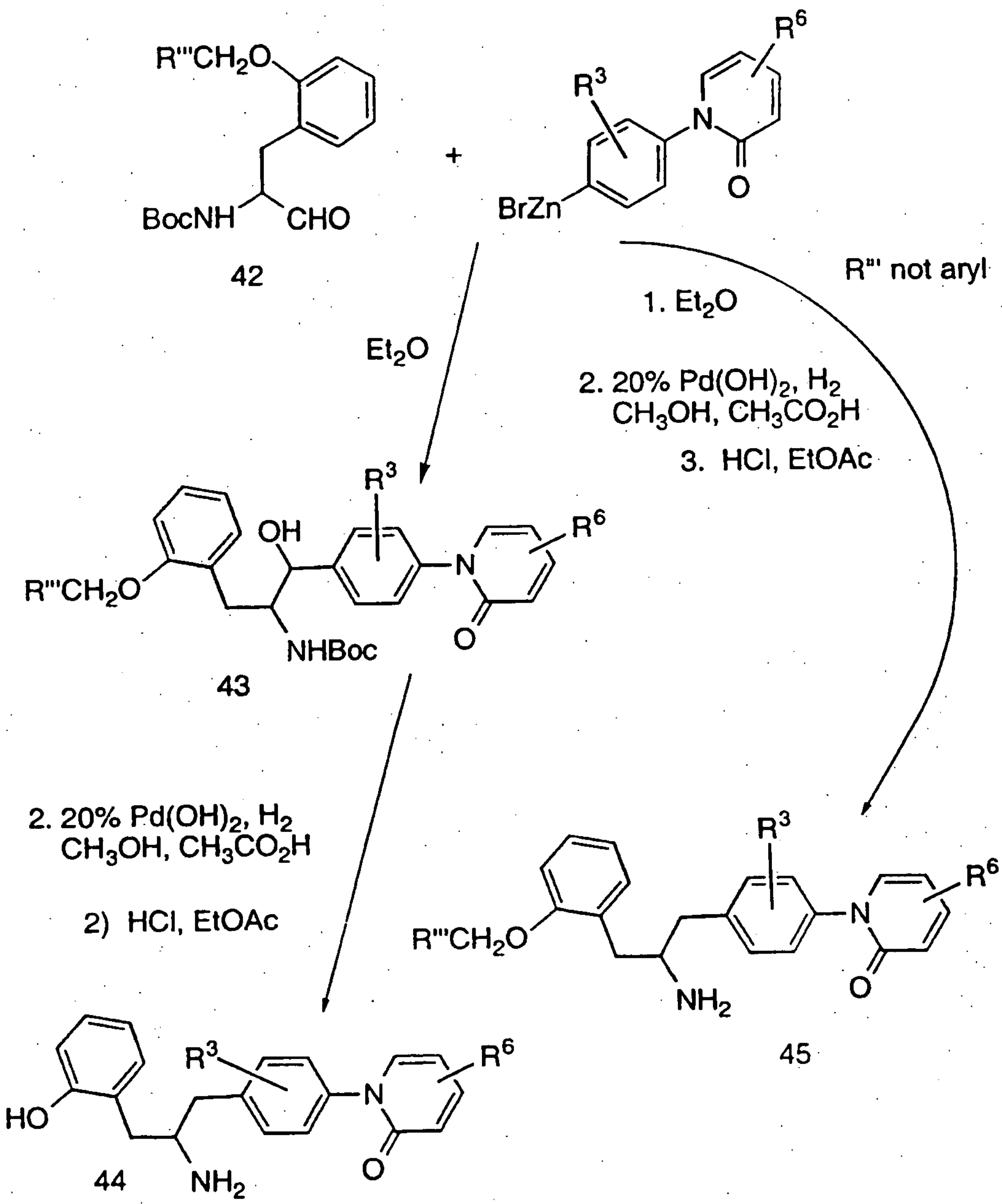
SCHEME 46


R3
R6
HO
NHBoc
N
O
36
CF3CO2H
CH2Cl2
R3
R6
HO
NH2
N
O
38
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
R3
R6
HO
NH
R'CH2
N
O
39

SCHEME 48


HO
H_2N
CO_2H
1) Boc_2O, K_2CO_3
THF-H_2O
2) CH_2N_2, EtOAc
HO
BocNH
CO_2CH_3
$LiAlH_4$
THF
0-20°C
HO
BocNH
CH_2OH
R'''CH_2X
Cs_2CO_3
DMF
R'''CH_2O
BocNH
CH_2OH
pyridine · SO_3
DMSO
$(C_2H_5)_3N$
20°C
R'''CH_2O
BocNH
CHO

SCHEME 48 (continued)



The compounds of the formula (III) are prepared by employing reactions as shown in the Schemes 49-61, in addition to other standard manipulations such as ester hydrolysis, cleavage

of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R^3, R^6 and R^8, as shown in the Schemes, represent the substituents R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^{6e} and R^8; although only one such R^3, R^6 or R^8 is present in the intermediates and products of the schemes, it is understood that the reactions shown are also applicable when such aryl or heterocyclic moieties contain multiple substituents. The compounds referred to in the Synopsis of Schemes 49-61 are numbered starting sequentially with 1 and ending with 42.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes. The reactions described in the Schemes are illustrative only and are not meant to be limiting. Other reactions useful in the preparation of heteroaryl moieties are described in "Comprehensive Organic Chemistry, Volume 4: Heterocyclic Compounds" ed. P.G. Sammes, Oxford (1979) and references therein.

<u>Synopsis of Schemes 49-61:</u>

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Schemes 49-56 illustrate synthesis of the instant bicyclic compounds which incorporate a preferred benzylimidazolyl sidechain. Thus, in Scheme 49, for example, a bicyclic intermediate that is not commercially available may be synthesized by methods known in the art. Thus, a suitably substituted pyridinonyl alcohol **2** may be synthesized starting from the corresponding isonicotinate **1** according to procedures described by Boekelhiede and Lehn (*J. Org. Chem.*, 26:428-430 (1961)). The alcohol is then protected and reacted under Ullmann coupling conditions with a suitably substituted phenyl iodide, to provide the intermediate bicyclic alcohol **3**. The intermediate alcohol **3** may converted to the corresponding bromide **4**. The bromide **4** may be coupled to a suitably substituted

benzylimidazolyl **5** to provide, after deprotection, the instant compound **6**.

Schemes 50-52 illustrate methods of synthesizing related or alcohol intermediates, which can then be processed as described in Scheme 49. Thus, Scheme 50 illustrates preparation of a pyridylpyridinonyl alcohol and thienylpyridinonyl alcohol starting with the suitably substituted halogenated heterocycles.

Scheme 51 illustrates preparation of the intermediate bromide **9** wherein the preferred pyridinone is replced by a saturated lactam. Acylation of a suitably substituted aniline **7** with a suitably substituted brominated acyl chloride provides the acylated intermediate **8**. Closure of the lactam ring provides the intermediate alcohol, which is converted to the bromide as described above.

Scheme 52 illustrates synthesis of an instant compound wherein a non-hydrogen R^{9b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **10** may be selectively iodinated to provide the 5-iodoimidazole **11**. That imidazole **11** may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **12**. Intermediate **12** can then undergo the alkylation reactions that were described hereinabove.

Scheme 53 illustrates synthesis of instant compounds that incorporate a preferred imidazolyl moiety connected to the biaryl via an alkyl amino, sulfonamide or amide linker. Thus, the 4-aminoalkylimidazole **13**, wherein the primary amine is protected as the phthalimide, is selectively alkylated then deprotected to provide the amine **14**. The amine **14** may then react under conditions well known in the art with various activated arylheteroaryl moieties to provide the instant compounds shown.

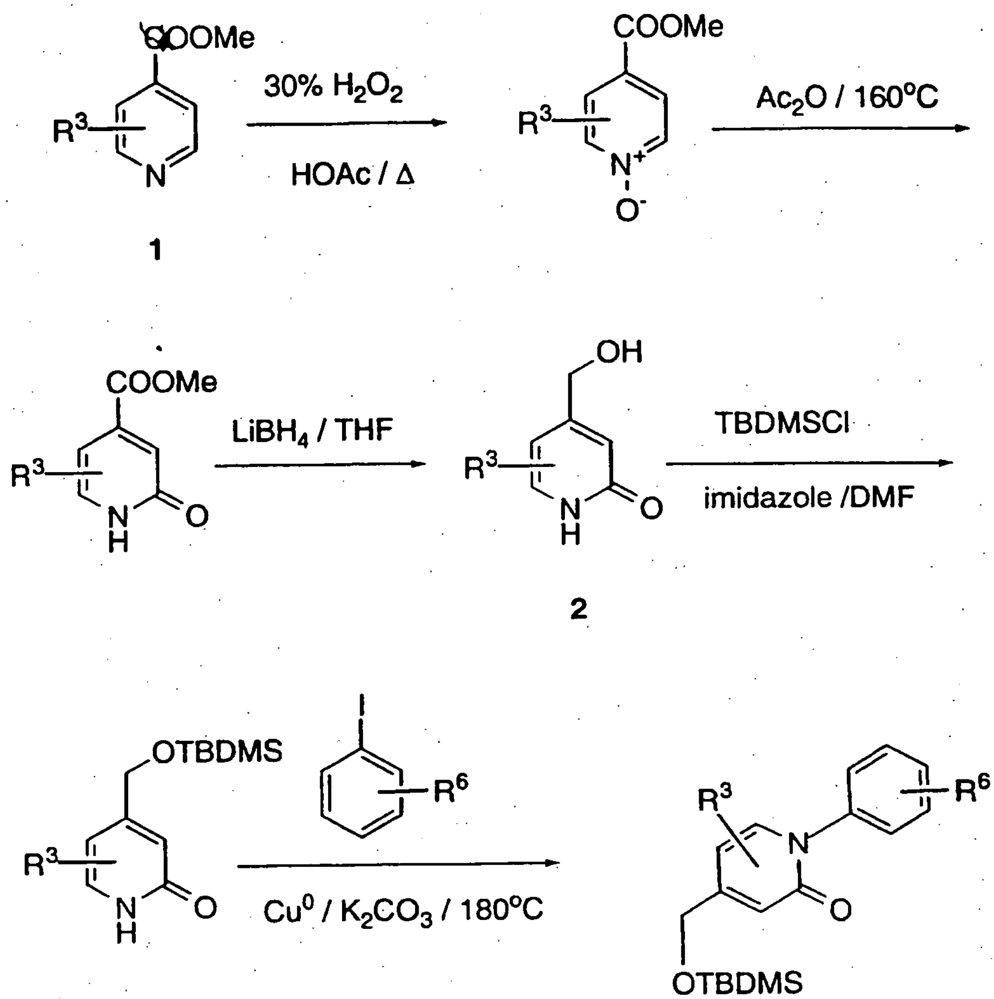
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 54. The suitably substituted phenol **15** may be reacted with methyl

N-(cyano)methanimidate to provide the 4-phenoxyimidazole **16**. After selective protection of one of the imidazolyl nitrogens, the intermediate **17** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

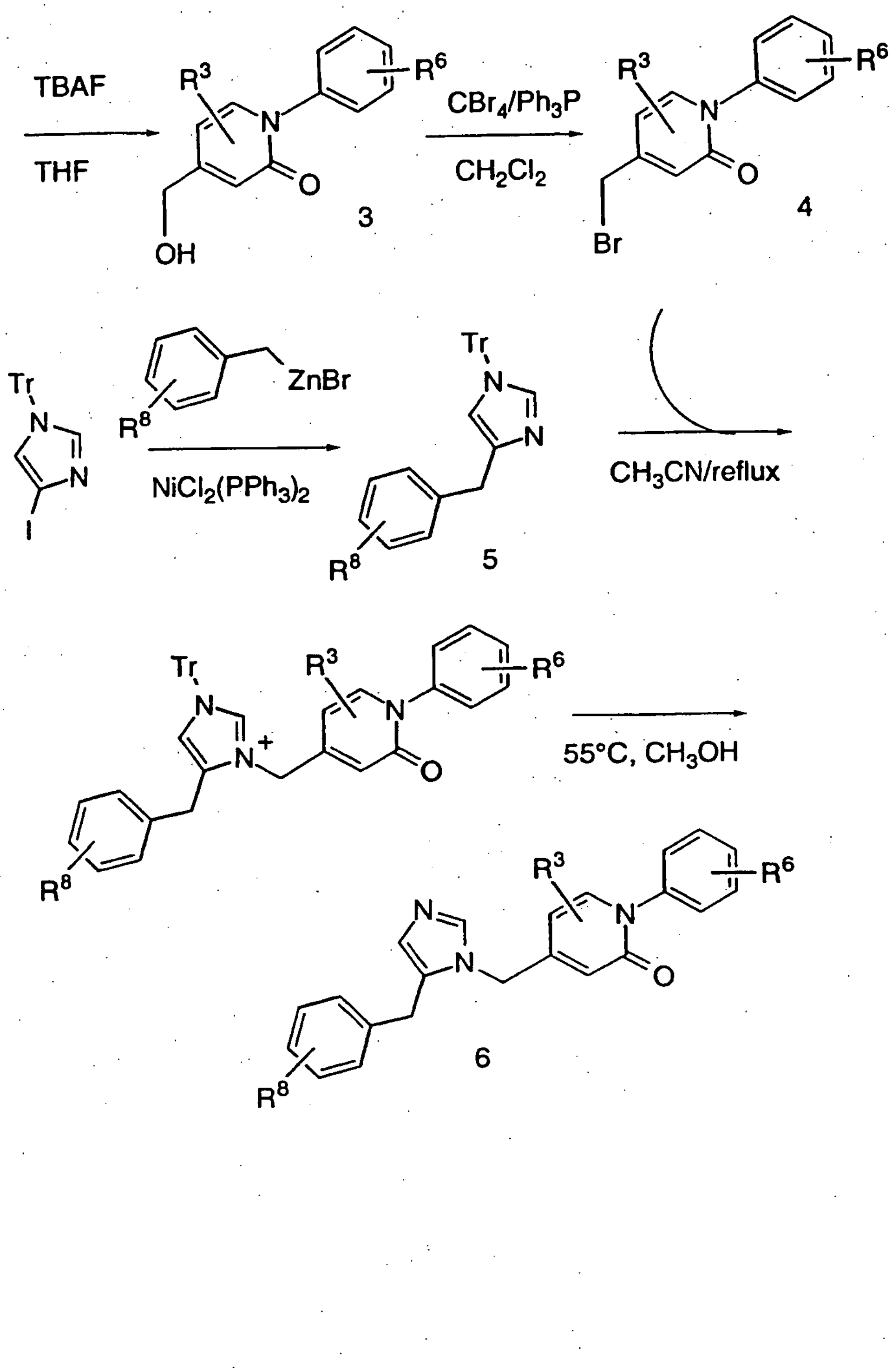
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 55. Thus, the N-protected imidazolyl iodide **18** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **19**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 49) provides the instant compound **20**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 56 illustrates incorporation of an acetyl moiety as the $(CR^2{}_2)_pX(CR^2{}_2)_p$ linker of the instant compounds. Thus, the suitably substituted acetyl pyridine **21** is converted to the corresponding pyridinone and undergoes the Ullmann reaction with a suitably substituted phenyl iodide. The acetyl is then brominated to provide intermediate **22**. Reaction with the imidazolyl reagent **5** provides, after deprotection, the instant compound **23**.

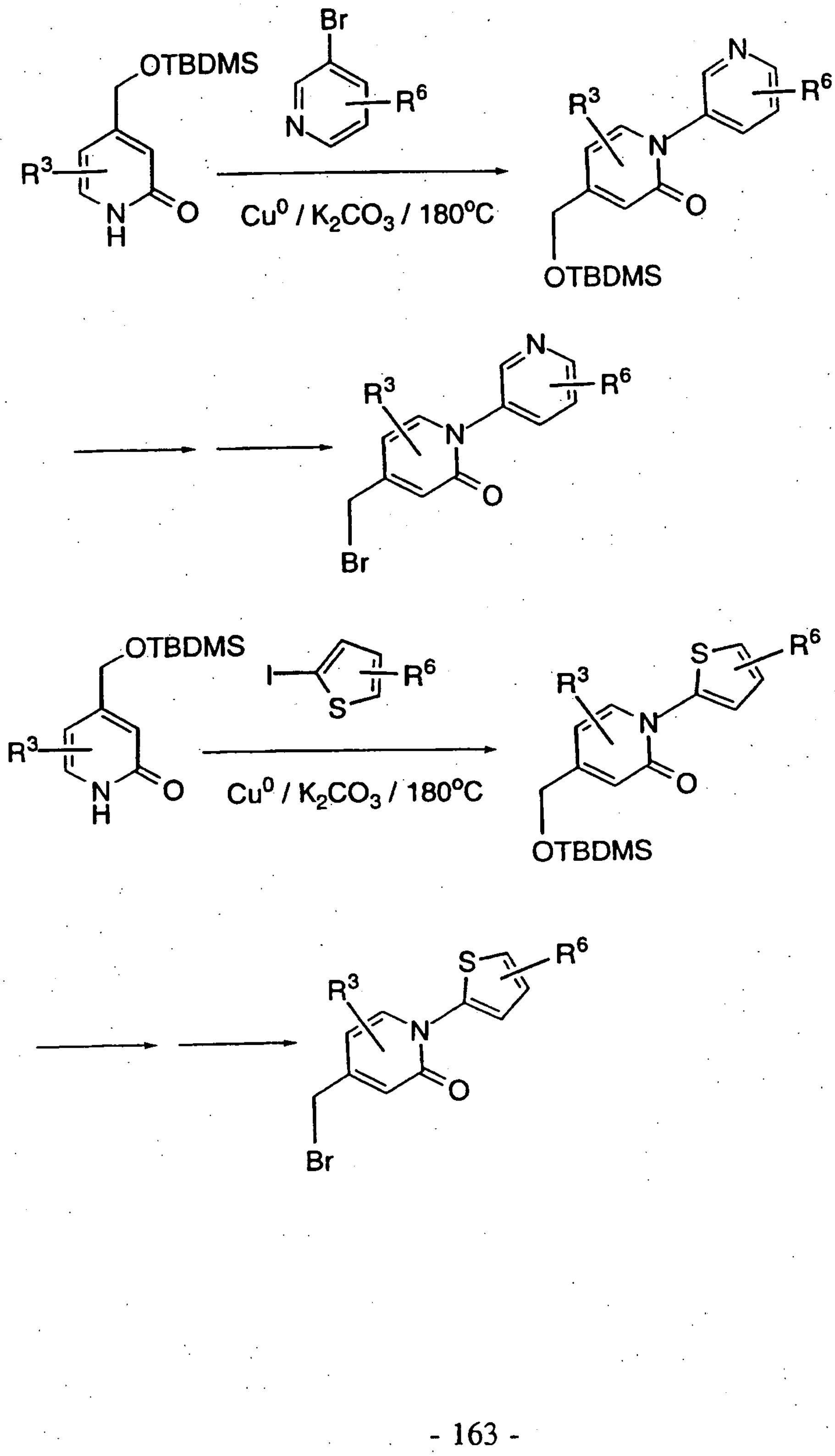
SCHEME 49



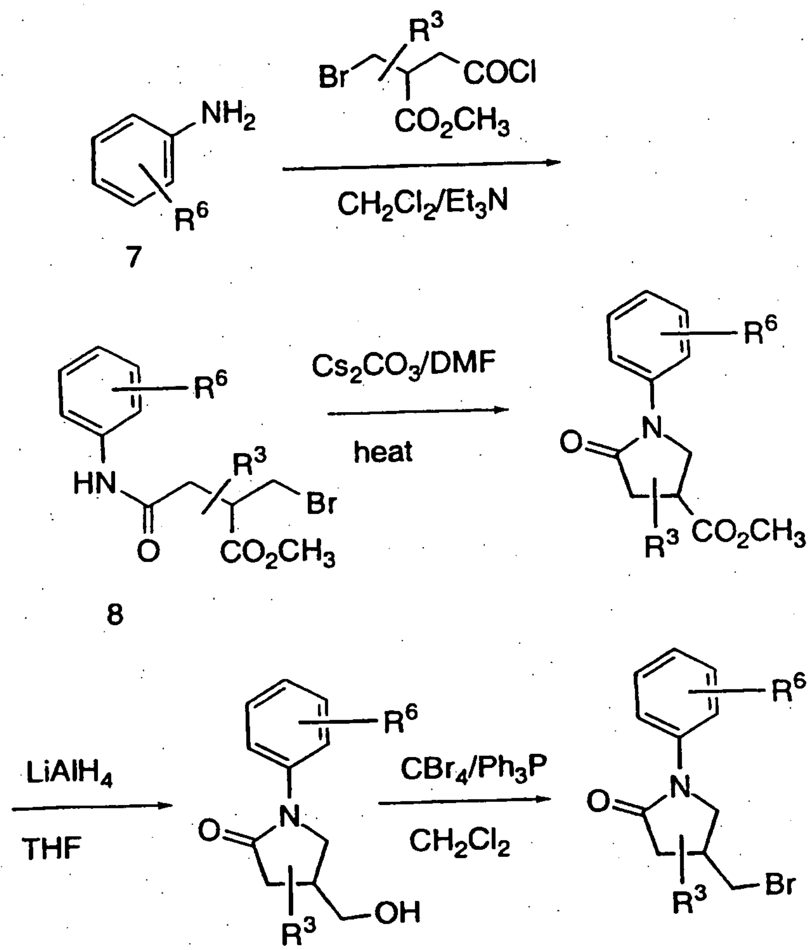
SCHEME 49 (continued)



SCHEME 50

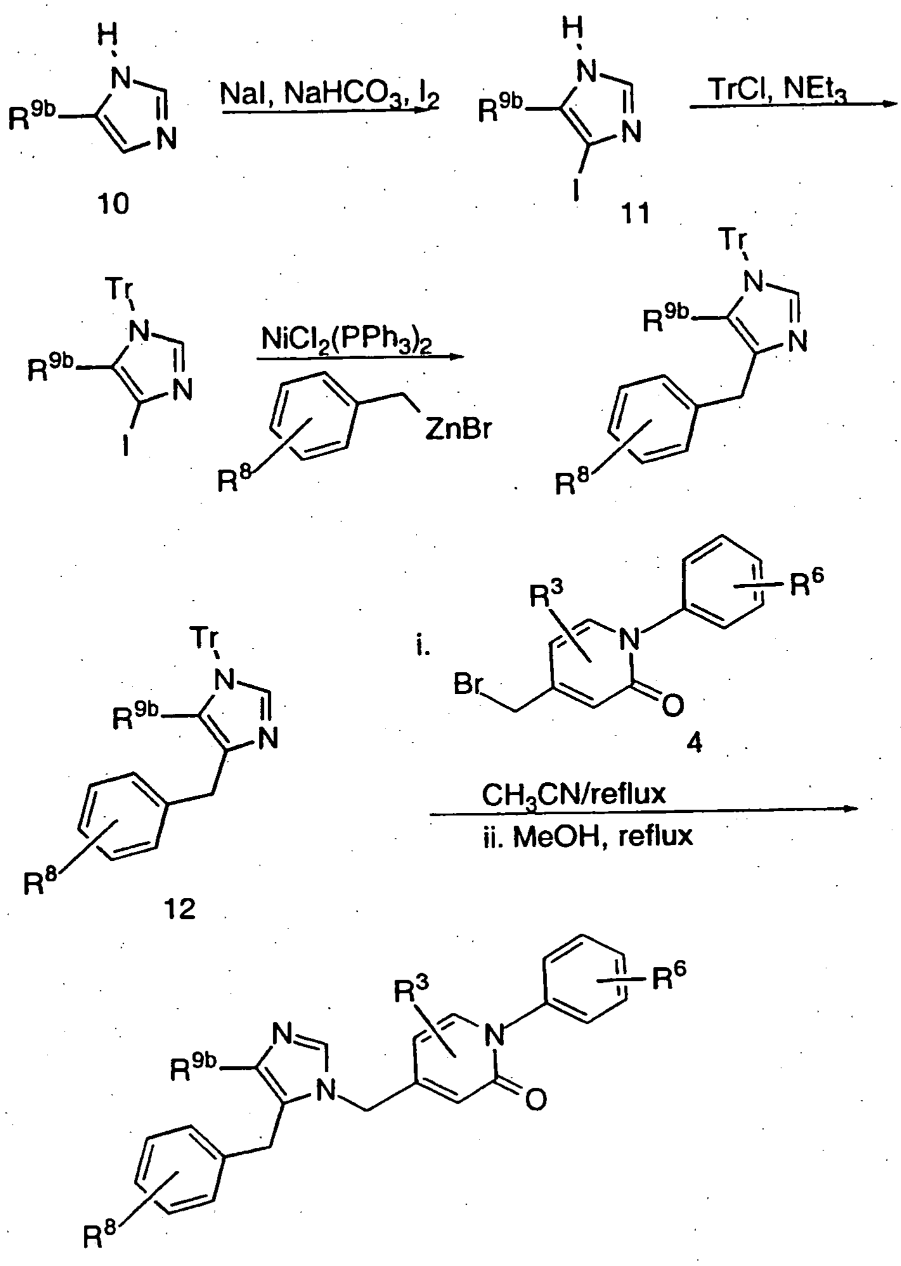

OTBDMS
Br
R6
N
R3
N
H
O
Cu0 / K2CO3 / 180°C
N
R3
R6
N
O
OTBDMS
N
R3
R6
N
O
Br
OTBDMS
I
S
R6
R3
N
H
O
Cu0 / K2CO3 / 180°C
S
R6
R3
N
O
OTBDMS
S
R6
R3
N
O
Br

SCHEME 3

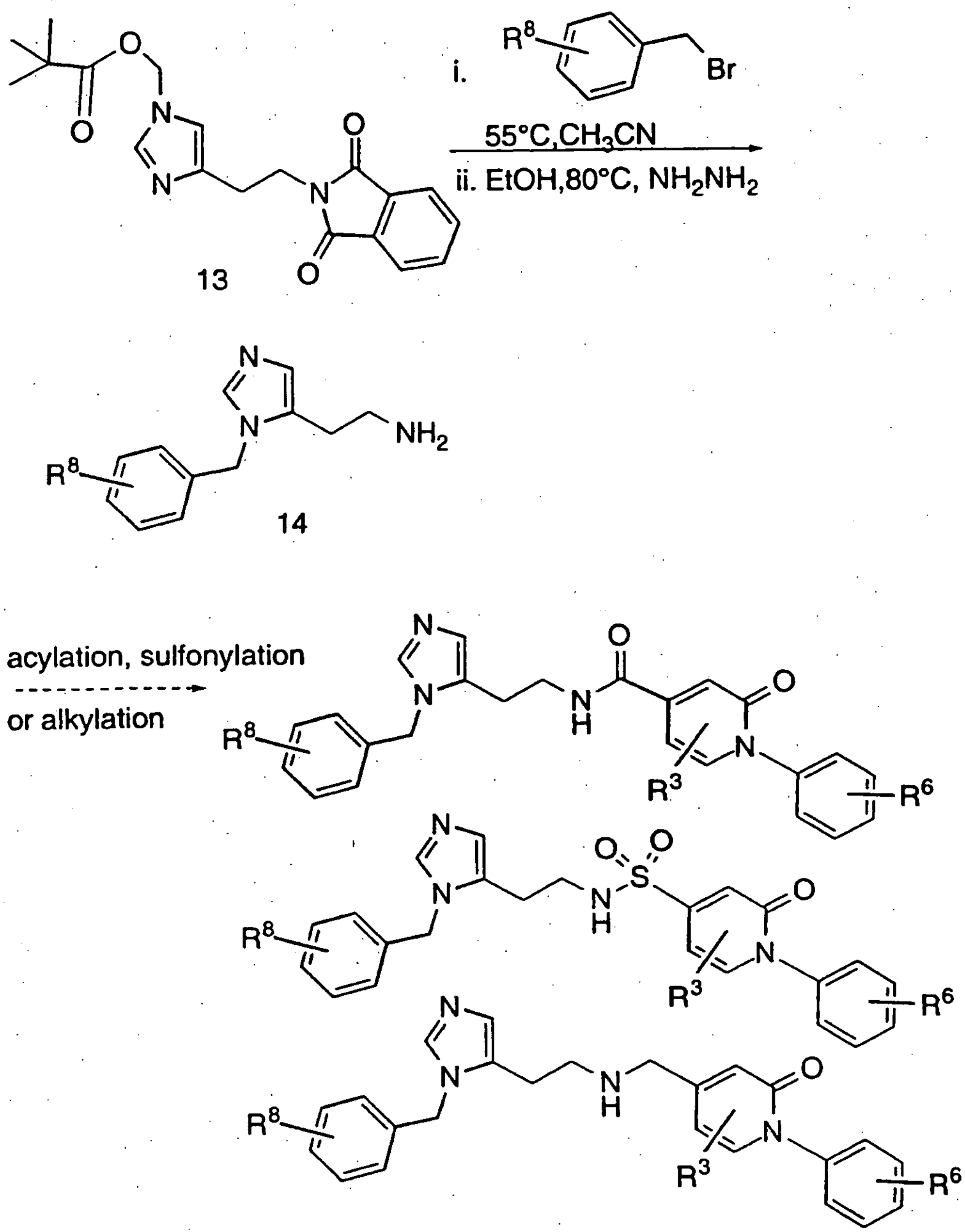


NH2
R6
7
R3
Br
COCl
CO2CH3
CH2Cl2/Et3N
R6
HN
R3
Br
O
CO2CH3
8
Cs2CO3/DMF
heat
R6
O
N
R3
CO2CH3
LiAlH4
THF
R6
O
N
R3
OH
CBr4/Ph3P
CH2Cl2
R6
O
N
R3
Br
9

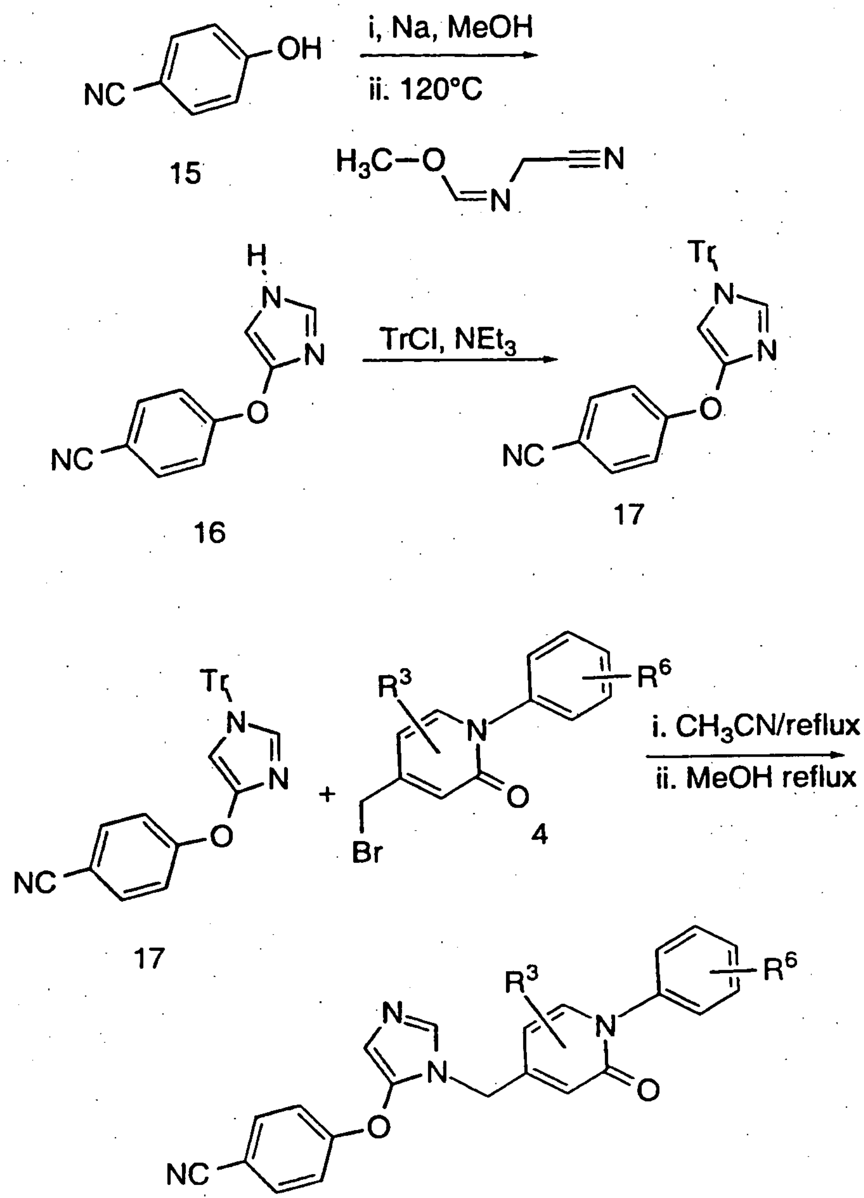
SCHEME 52


H
N
N
R9b
10
NaI, NaHCO3, I2
H
N
N
R9b
I
11
TrCl, NEt3
Tr
N
N
R9b
I
NiCl2(PPh3)2
ZnBr
R8
Tr
N
N
R9b
R8
Tr
N
N
R9b
R8
12
i.
R3
N
R6
Br
O
4
CH3CN/reflux
ii. MeOH, reflux
N
R9b
N
R3
N
R6
O
R8

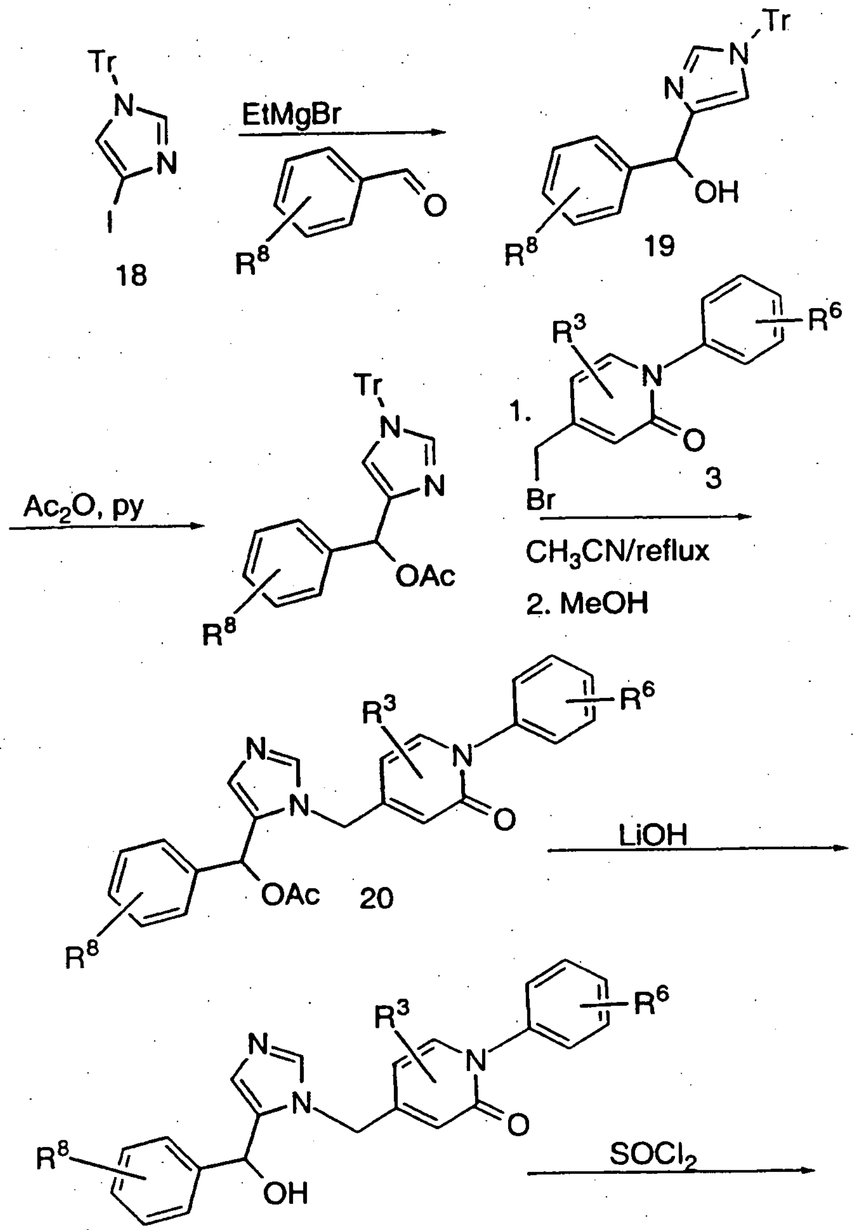
SCHEME 53


R8
i.
Br
55°C,CH3CN
ii. EtOH,80°C, NH2NH2
13
14
NH2
acylation, sulfonylation
or alkylation
R3
R6

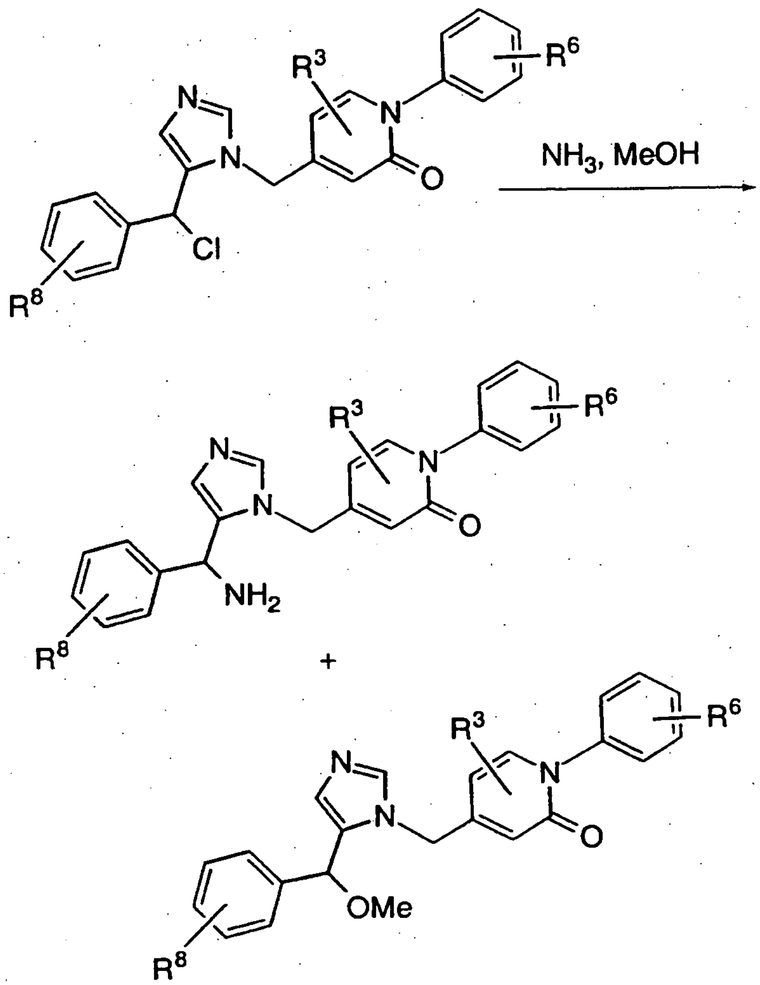
SCHEME 54


NC
OH
i, Na, MeOH
ii. 120°C
15
H3C–O
N
≡N
H
N
N
O
NC
TrCl, NEt3
Tr
N
N
O
NC
16
17
Tr
N
N
O
NC
+
R3
N
R6
O
Br
4
i. CH3CN/reflux
ii. MeOH reflux
17
N
N
O
NC
R3
N
R6
O

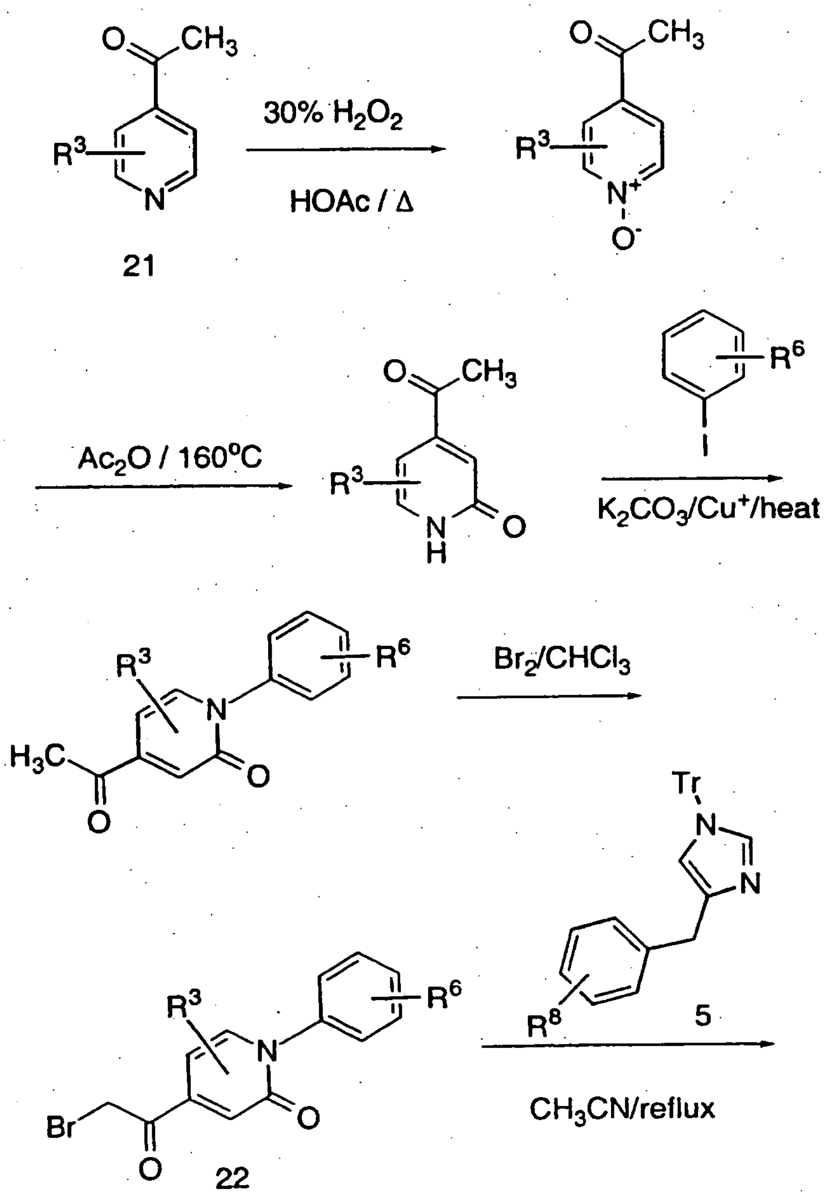
SCHEME 55


Tr
N
N
I
18
EtMgBr
O
R8
Tr
N
N
OH
R8
19
Ac2O, py
Tr
N
N
OAc
R8
R3
N
R6
1.
O
Br
3
CH3CN/reflux
2. MeOH
R3
N
R6
N
N
O
OAc
20
R8
LiOH
R3
N
R6
N
N
O
R8
OH
SOCl2

SCHEME 55 (continued)

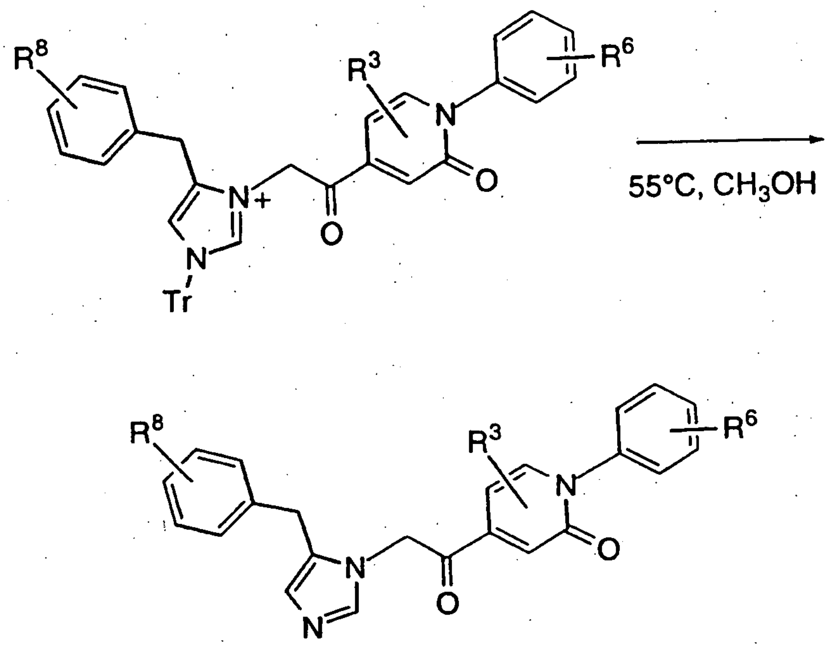


SCHEME 56



30% H_2O_2
HOAc / Δ
21
Ac_2O / 160°C
K_2CO_3/Cu^+/heat
Br_2/$CHCl_3$
22
5
CH_3CN/reflux

SCHEME 56 (continued)



23

Schemes 57-61 illustrate reactions wherein the moiety

$$\begin{array}{l}(R^8)_r \\ \quad | \\ V - A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n\end{array}\left(\begin{array}{c}(R^9)_q \\ | \\ W\end{array}\right)_t - (CR^1{}_2)_p\text{-}X$$

incorporated in the compounds of the instant invention is represented by other than a substituted imidazole-containing group.

Thus, the intermediates whose synthesis are illustrated in the Schemes, and other pyridinonecarbocyclic and pyridinonehetero-cyclic intermediates obtained commercially or readily synthesized, can be coupled with a variety of aldehydes. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in <u>Organic Syntheses</u>, **1988**,

67, 69-75, from the appropriate amino acid. Knochel chemistry may be utilized, as shown in Scheme 57, to incorporate the aryl-pyridinone moiety. Thus, a suitably substituted 4-(bromo)pyridine is converted to the corresponding pyridinone **24** as described above and the pyridinone is coupled to a suitably substituted phenyl iodide as previously described above. The resulting bromide **25** is treated with zinc(0) and the resulting zinc bromide reagent **26** is reacted with an aldehyde to provide the C-alkylated instant compound **27**. Compound **27** can be deoxygenated by methods known in the art, such as a catalytic hydrogention, then deprotected with trifluoro-acetic acid in methylene chloride to give the final compound **28**. The compound **28** may be isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **28** can further be selectively protected to obtain **29**, which can subsequently be reductively alkylated with a second aldehyde to obtain compound **30**. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole **31** can be accomplished by literature procedures.

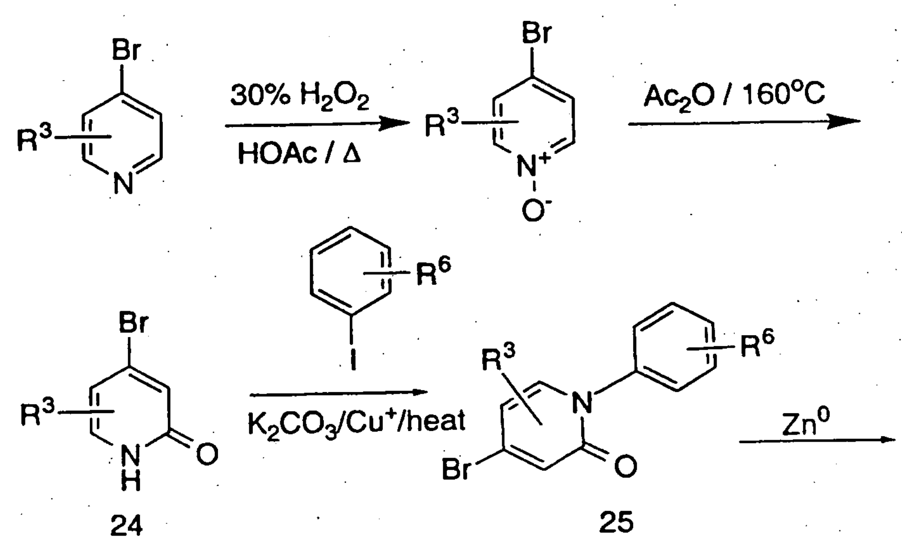
If the arylpyridinone zinc bromide reagent is reacted with an aldehyde which also has a protected hydroxyl group, such as **32** in Scheme 58, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 58, 59). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then be reacted with a variety of organometallic reagents such as alkyl lithium reagents, to obtain secondary alcohols such as **34**. In addition, the fully deprotected amino alcohol **35** can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as **36** (Scheme 59), or tertiary amines.

The Boc protected amino alcohol **33** can also be utilized to synthesize 2-aziridinylmethylarylheteroaryl such as **37** (Scheme 60). Treating **33** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of

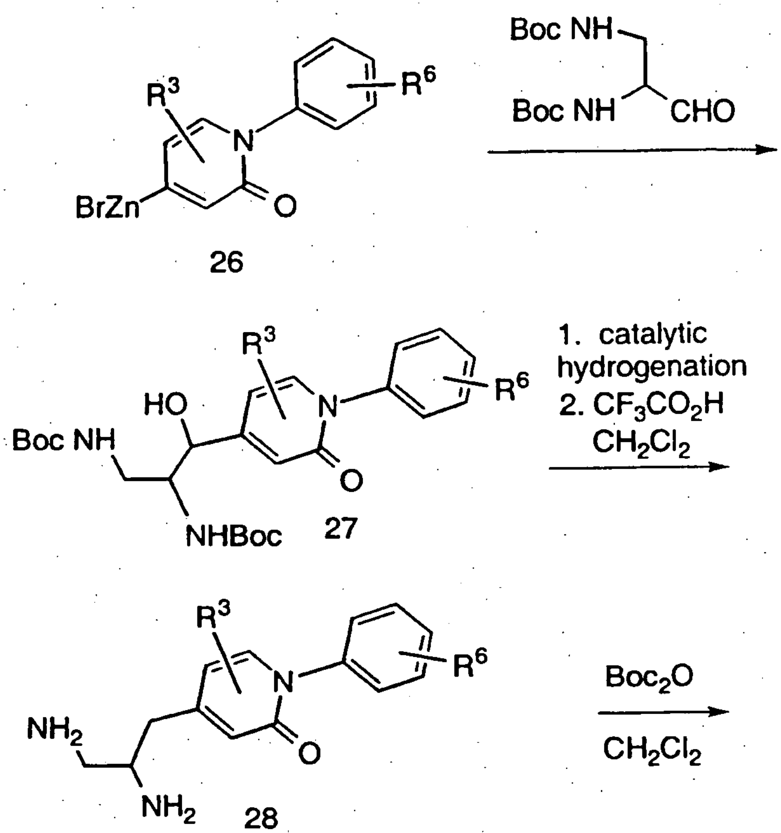
aziridine **37**. The aziridine is reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product **38** .

In addition, the arylpyridinone reagent can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as **40**, as shown in Scheme 61. When R' is an aryl group, **40** can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce **41**. Alternatively, the amine protecting group in **40** can be removed, and O-alkylated phenolic amines such as **42** produced.

SCHEME 57



SCHEME 57 (continued)

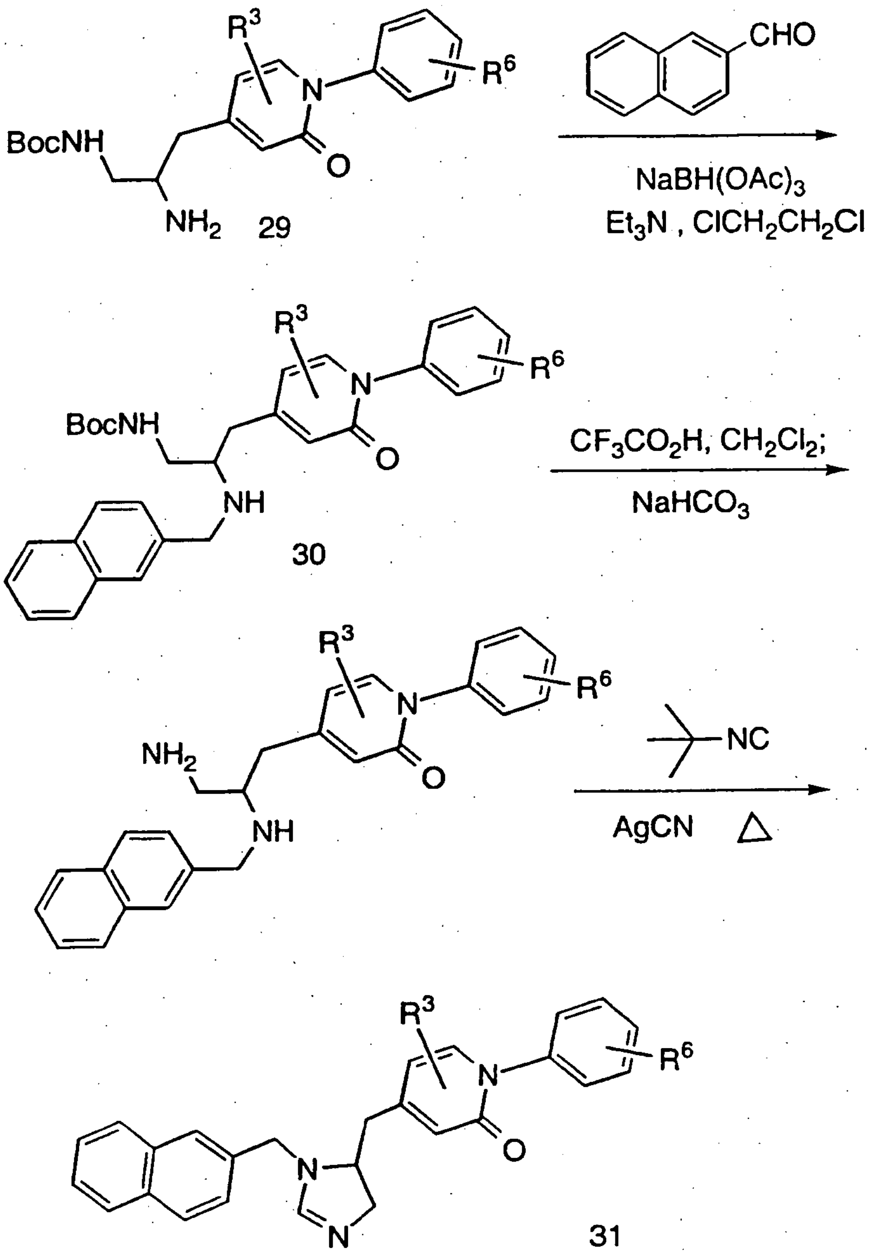


26

27

28

SCHEME 57 (continued)

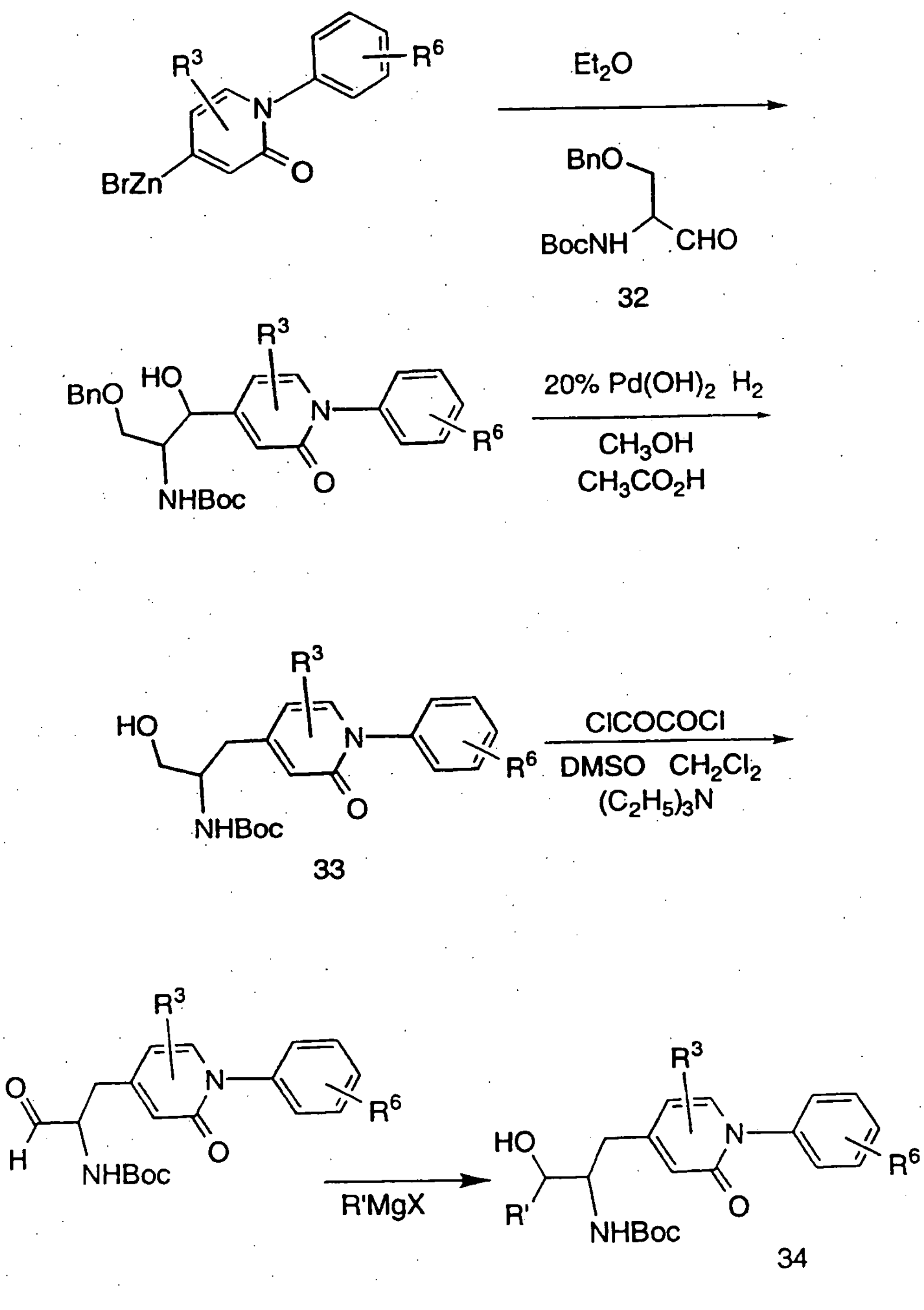


29

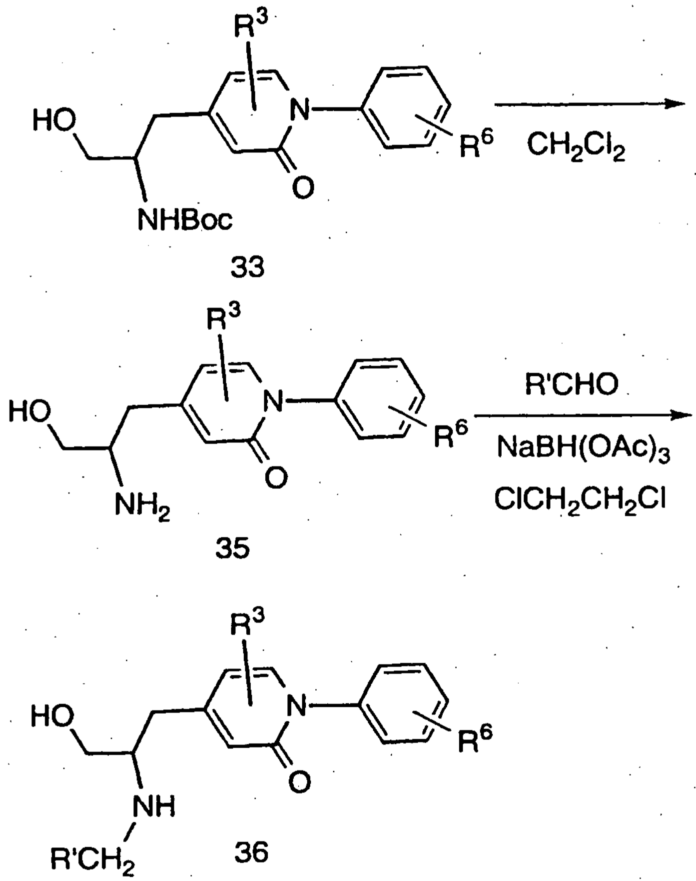
30

31

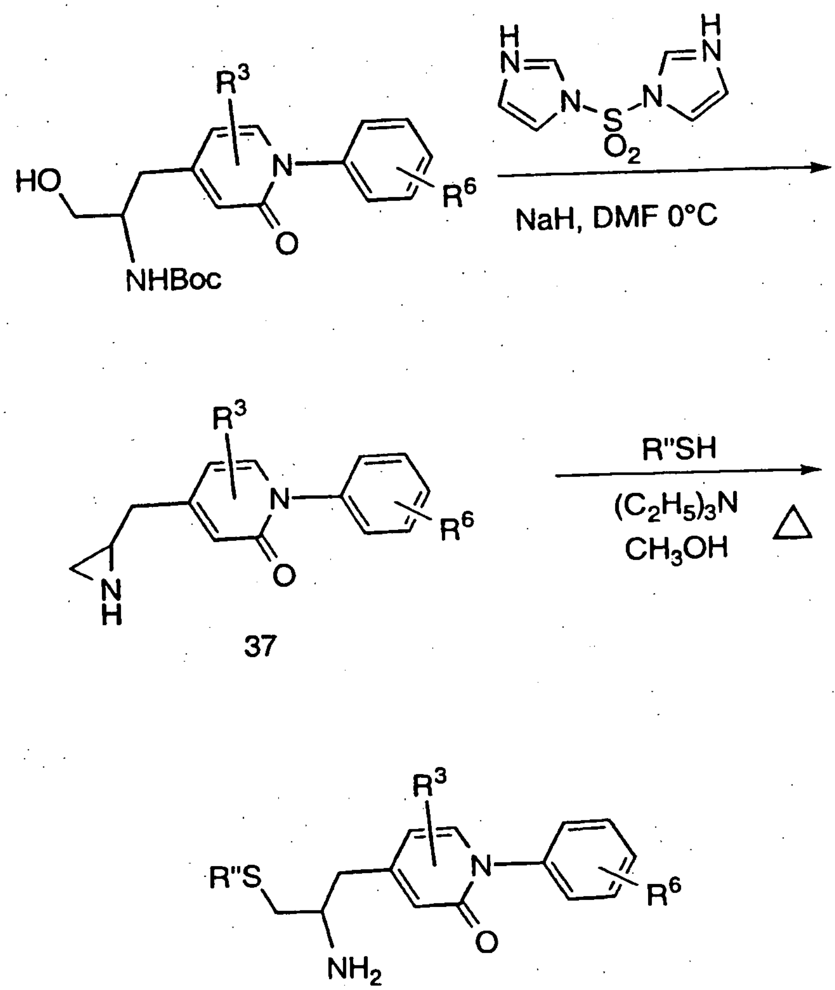
SCHEME 58


R3
R6
N
O
BrZn
Et2O
BnO
BocNH
CHO
32
HO
NHBoc
20% Pd(OH)2 H2
CH3OH
CH3CO2H
CICOCOCI
DMSO CH2Cl2
(C2H5)3N
33
H
R'MgX
R'
34

SCHEME 59


R3
HO
N
R6
O
NHBoc
CH2Cl2
33
R3
HO
N
R6
O
NH2
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
35
R3
HO
N
R6
O
NH
R'CH2
36

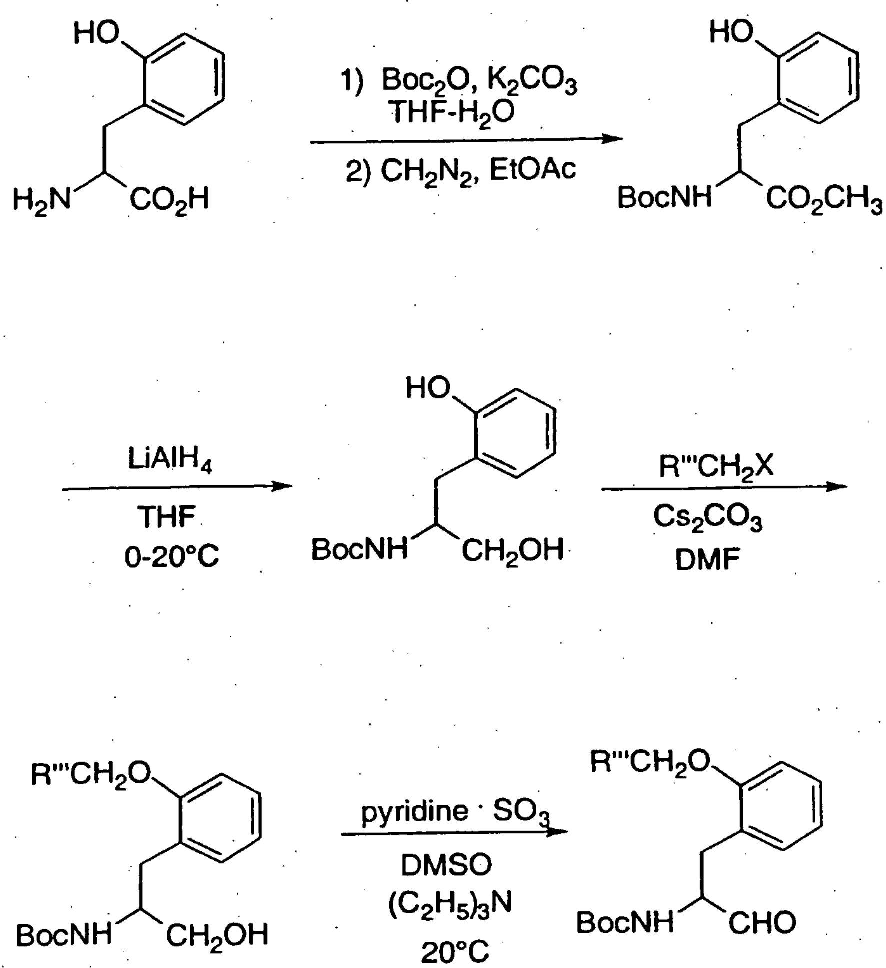
SCHEME 60



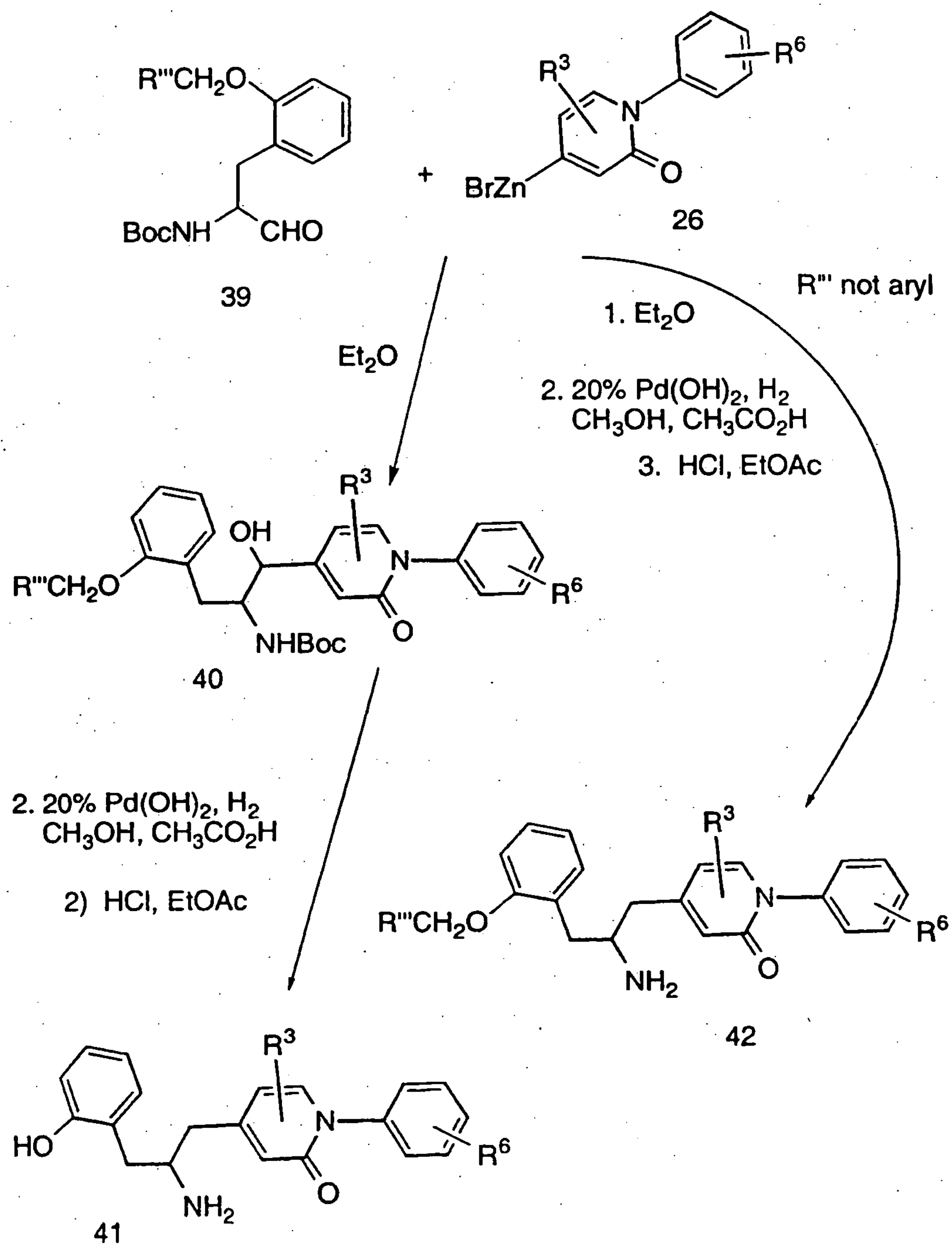
37

38

SCHEME 61


HO
H2N CO2H
1) Boc2O, K2CO3
THF-H2O
2) CH2N2, EtOAc
HO
BocNH CO2CH3
LiAlH4
THF
0-20°C
HO
BocNH CH2OH
R'''CH2X
Cs2CO3
DMF
R'''CH2O
BocNH CH2OH
pyridine · SO3
DMSO
(C2H5)3N
20°C
R'''CH2O
BocNH CHO

SCHEME 61 (continued)



The compounds of the formula (VII) are prepared by employing reactions as shown in the Schemes 62-72, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. While stereochemistry is shown in the Schemes, a person of ordinary skill in the art would understand that the illustrated compounds represent racemic mixtures which may be separated at a subsequent purification step or may be utilized as the racemic mixture. The compounds referred to in the Synopsis of Schemes 62-72 are numbered starting sequentially with 1-20 and ending with 50-58.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the reductive alkylation or acylation reactions described in the Schemes.

Synopsis of Schemes 62-69:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Schemes 62-64, for example, the syntheses of 1,3,5-trisubstituted piperidines are outlined. The reactions described therein may be similarly applied to suitably protected commercially available nipecotic acid or nipecotamide to provide compounds of the instant invention wherein R^3 is hydrogen.

As shown in Scheme 62, the pyridinedicarboxylic acid diester may be catalytically hydrogenated and then N-protected to provide a mixture of piperidine diesters **1**. The protected piperidine can then be partially hydrolyzed to provide a racemic mixture of 3,5-cis- and trans-isomers, that can be separated by chromatography. The remainder of Scheme 62 and Schemes 63 and 63 and 64 illustrate manipulation of the racemic mixture of the cis-isomers. It is well understood by one of ordinary skill in the art that such chemical manipulations can also be applied to the racemic mixture of the

trans-isomers to obtain other compounds of the instant invention. Furthermore, such manipulations can also be applied to enantiomerically pure isomers (i.e., the (+)-cis isomer or the (-)-cis isomer). The trans-isomer may also be epimerized to the cis-isomer by treatment with a base, such as sodium carbonate. Racemic final compounds may be separated on a chiral preparative HPLC column to give their respective diastereomers.

The monocarboxylic acid **2** can be treated with an appropriately substituted amine in the presence of a suitable coupling reagent, such as EDC/HOBT, and the like, to provide the 5-carboxy-nipecotamide **3**. The suitably substituted 5-carboxynipecotamide is then deprotected and the piperidine nitrogen can then be reductively alkylated to provide intermediate **4**. The remaining ester moiety is saponified and then similarly functionalized with another suitably substituted amine to provide the bisamidopiperidine **5**.

An alternative synthetic route to compound **5**, starting with the carboxynipecotamide **3**, is illustrated in Scheme 63.

As shown in Scheme 64, the monocarboxylic acid **2** can undergo a Curtius rearrangment to provide the piperidine **6** after catalytic reduction. Subsequent amide formation provides intermediate **7**, which is then subjected to the reactions illustrated in Scheme 62 to provide compound **8** of the instant invention.

The instant invention also includes 1,4-dihydropyridine and 1,2,3,4-tetrahydropyridine analogs of the piperidine compounds whose syntheses are described above. Scheme 65 illustrates the synthetic route to the intermediates **11** and **13** which correspond to the saturated ring intermedate **2** illustrated in Scheme 62. Thus, the appropriately substituted pyridine may be N-alkylated to provide the quaternary intermediate **9**. Subsequent reduction of this intermediate provides the 1,4-dihydropyridine **10**, which can be selectively hydrolized to the key intermediate **11**. Alternatively, the 1,4-dihydropyridine **10** can be further reduced to provide the enantiomeric mixture of tetrahydropyridines **12**, which can be hydrolized and resolved by chromatography to provide the key intermediate **13** (and the enantiomer

which is not illustrated). Intermediates **11** and **13** can then undergo synthetic modifications as described hereinabove in Schemes 62-64.

Schemes 66-68 illustrate the syntheses of 1,3-disubstituted piperidines of the instant invention wherein the "X" moiety is other than an amido moiety. The reactions illustrated therein may be modified by using appropriate protecting groups and reagents well known to one skilled in the art to provide 1,3,5-trisubstituted piperidines of the instant invention.

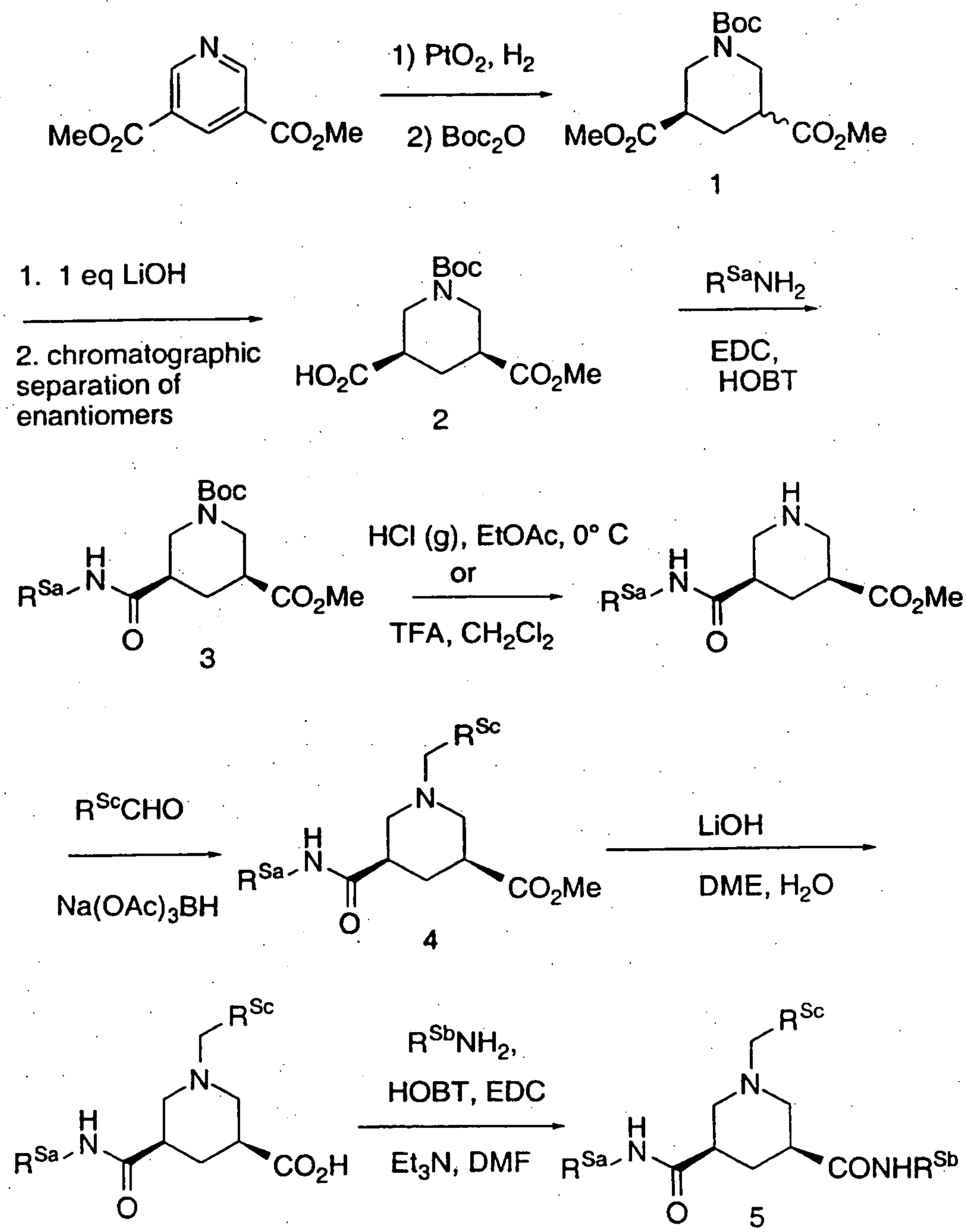
Scheme 66 illustrates the syntheses of compounds of the instant invention wherein "X" is -S- or $-SO_2-$. A racemic nipecotate **14** can be resolved by the selective crystallization of chiral tartrate salts and is then reductively alkylated to provide the ester **15**. Intermediate **15** is reduced to the alcohol **16**, activated and treated with a suitable thioacetate to provide the thioester **17**. The thiol is then generated and may be alkylated and optionally oxidized to provide compounds **18** and **19** of the instant invention.

The intermediate **16** may be selectively oxidized back to an aldehyde, which can then be utilized to reductively alkylate a suitably substituted amine to provide the instant compound **20**. The secondary amine of **20** can be further functionalized as illustrated in Scheme 67.

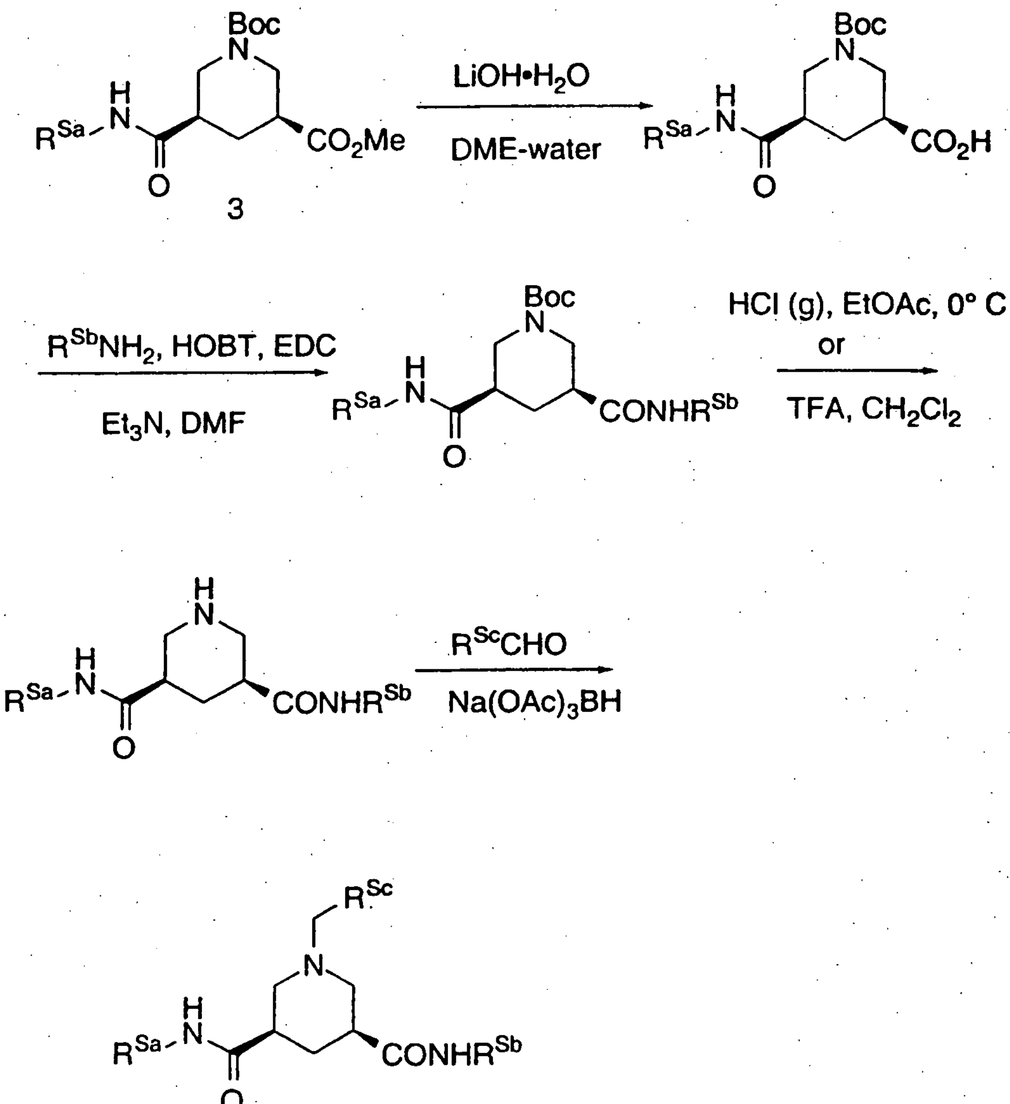
The activated alcohol can also be reacted with a suitably substituted imidazolyl to provide compounds of the instant invention wherein "X" is a bond, as shown in Scheme 68.

Scheme 69 illustrates the syntheses of compounds of the instant invention wherein R^2 is an aryl moiety.

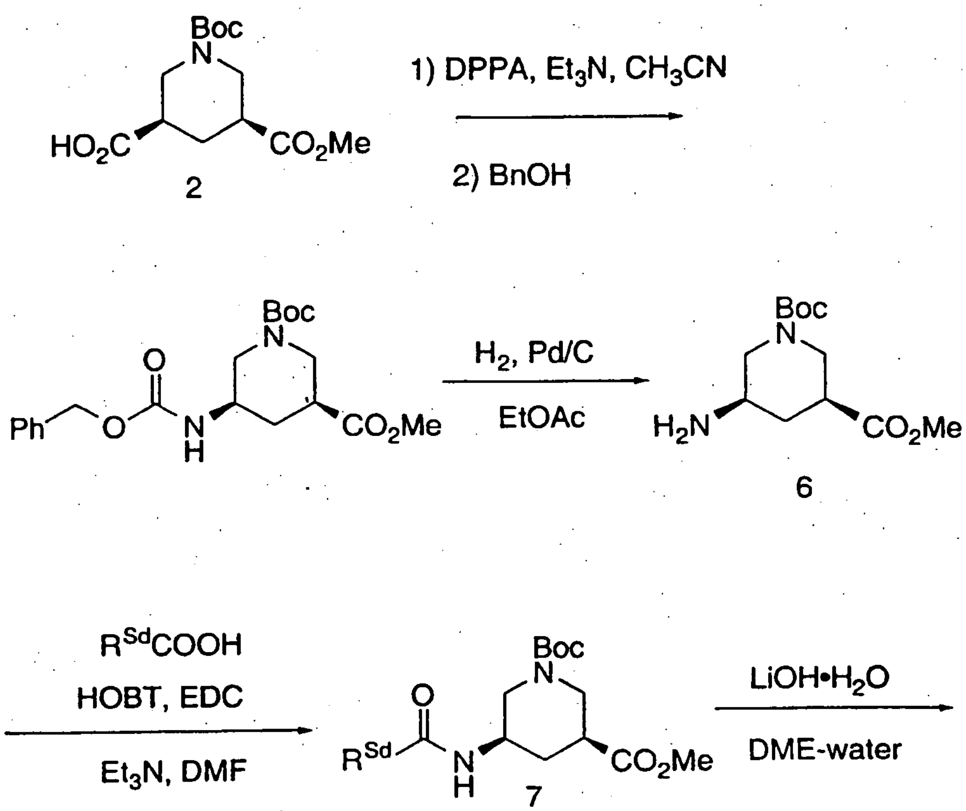
SCHEME 62



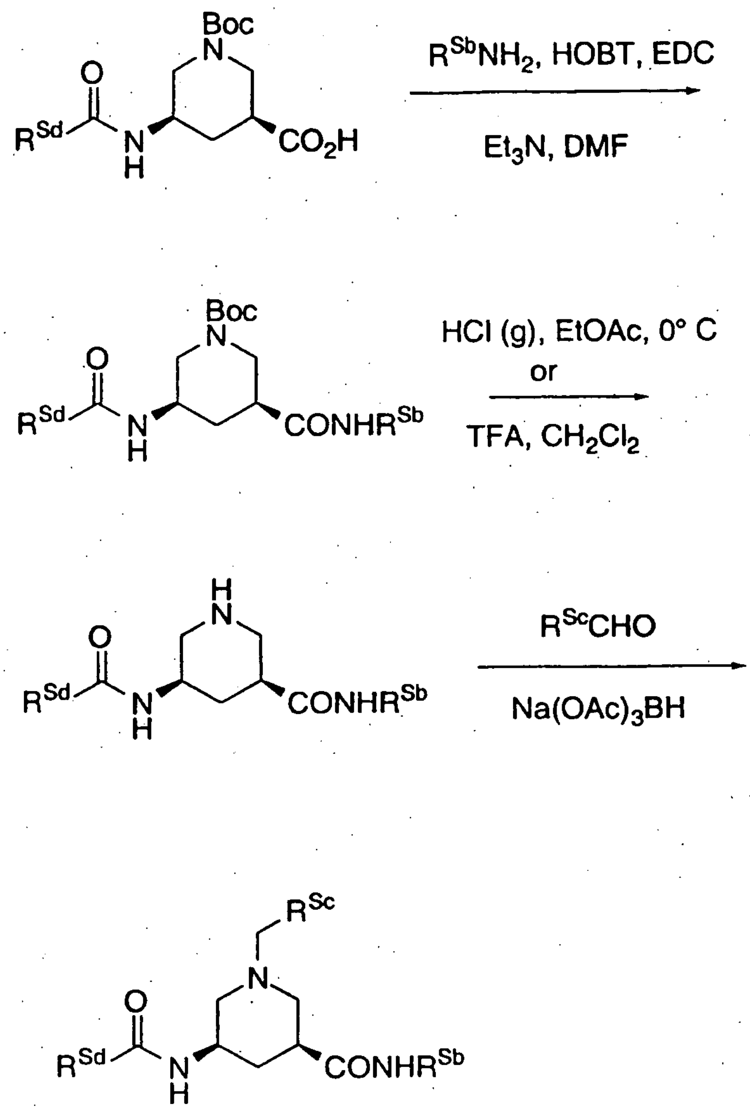
SCHEME 63


Boc
LiOH•H$_2$O
DME-water
CO$_2$Me
CO$_2$H
3
R^{Sb}NH$_2$, HOBT, EDC
Et$_3$N, DMF
CONHR^{Sb}
HCl (g), EtOAc, 0° C
or
TFA, CH$_2$Cl$_2$
R^{Sc}CHO
Na(OAc)$_3$BH
5

SCHEME 64

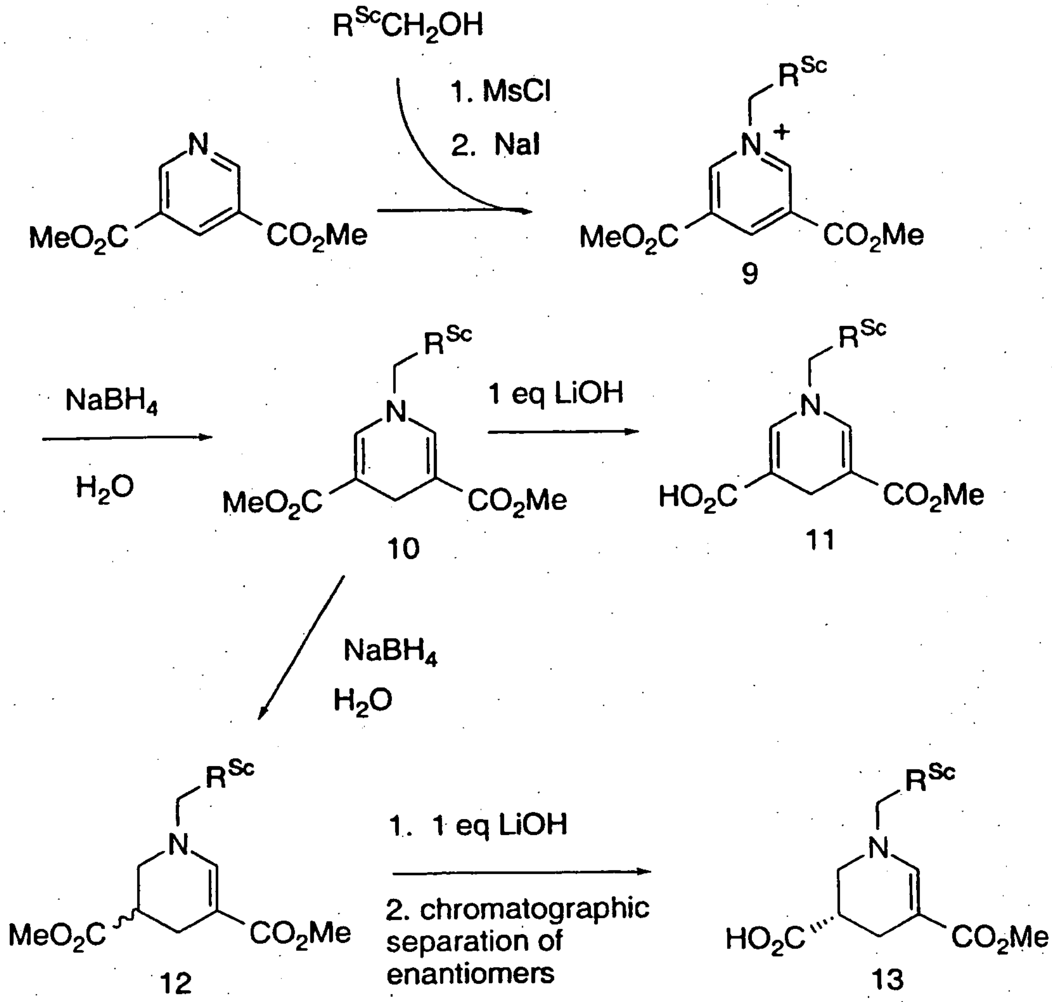

Boc
N
HO_2C
CO_2Me
2
1) DPPA, Et_3N, CH_3CN
2) BnOH
Ph
O
N
H
H_2, Pd/C
EtOAc
H_2N
6
$R^{Sd}COOH$
HOBT, EDC
Et_3N, DMF
R^{Sd}
7
LiOH•H_2O
DME-water

SCHEME 64 (continued)



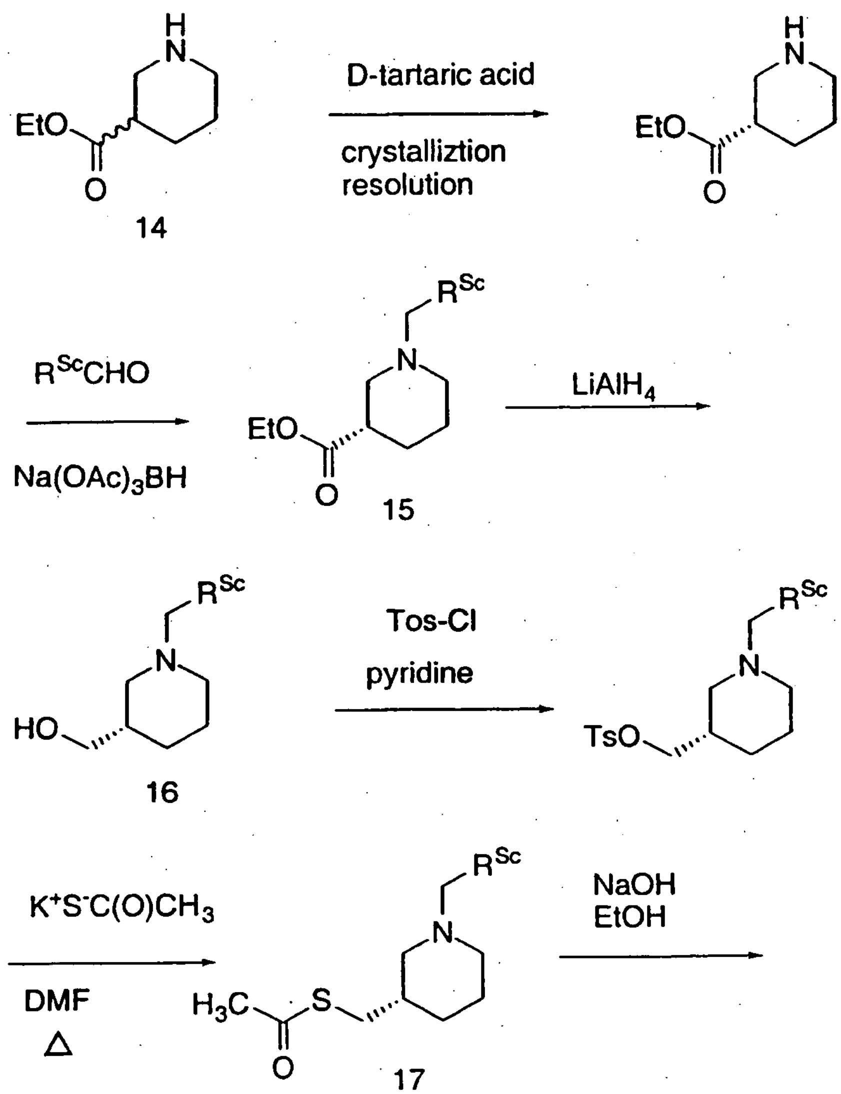
8

SCHEME 65



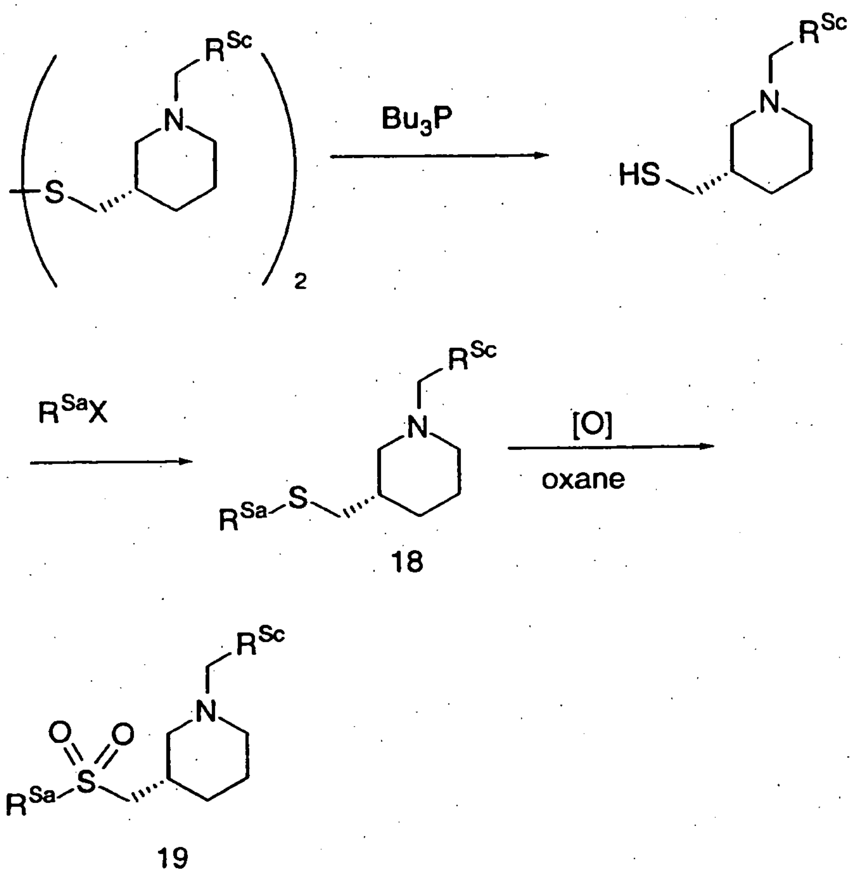
$R^{Sc}CH_2OH$
1. MsCl
2. NaI
MeO_2C
CO_2Me
R^{Sc}
9
$NaBH_4$
H_2O
10
1 eq LiOH
HO_2C
11
12
1. 1 eq LiOH
2. chromatographic separation of enantiomers
13

SCHEME 66

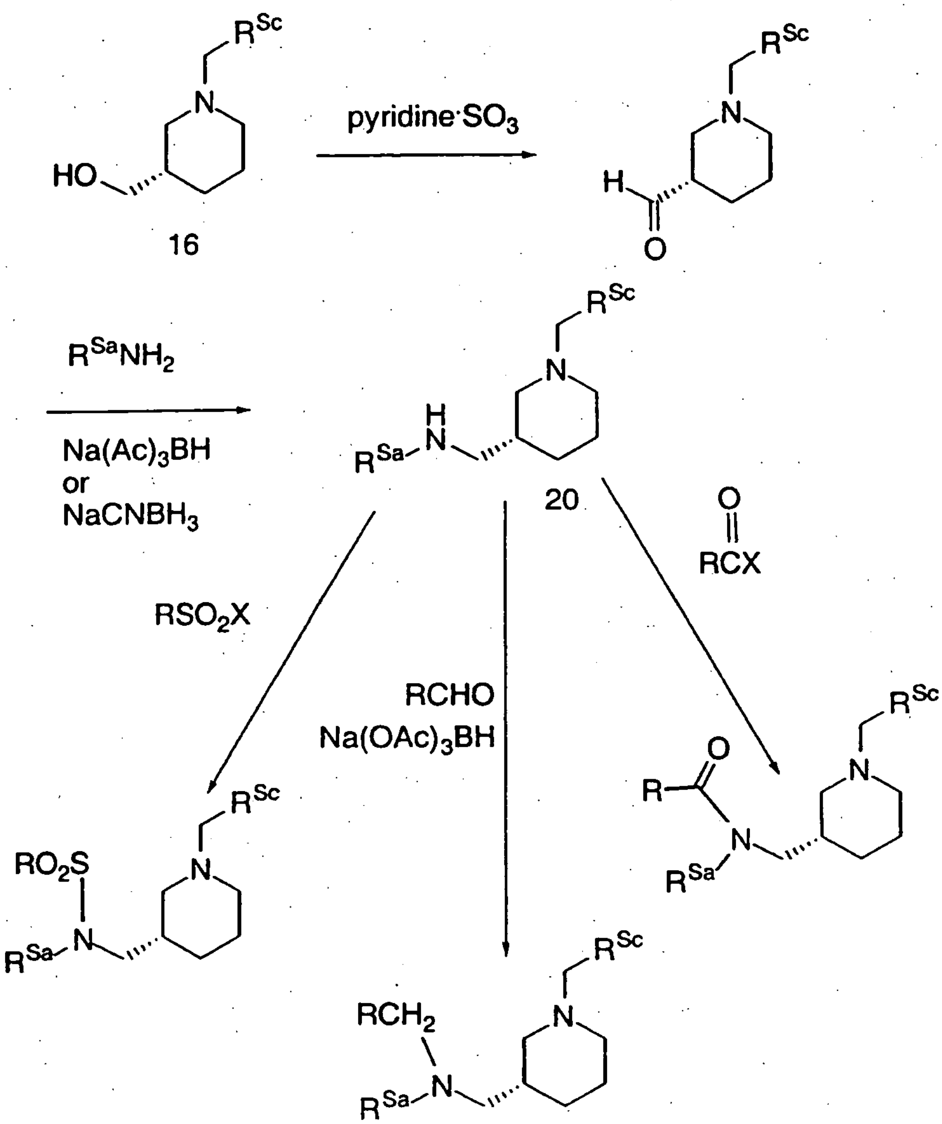


EtO
O
H
N
14
D-tartaric acid
crystalliztion
resolution
EtO
O
H
N
R^Sc CHO
Na(OAc)3BH
R^Sc
N
EtO
O
15
LiAlH4
R^Sc
N
HO
16
Tos-Cl
pyridine
R^Sc
N
TsO
K+S-C(O)CH3
DMF
Δ
R^Sc
N
H3C
S
O
17
NaOH
EtOH

SCHEME 66 (continued)

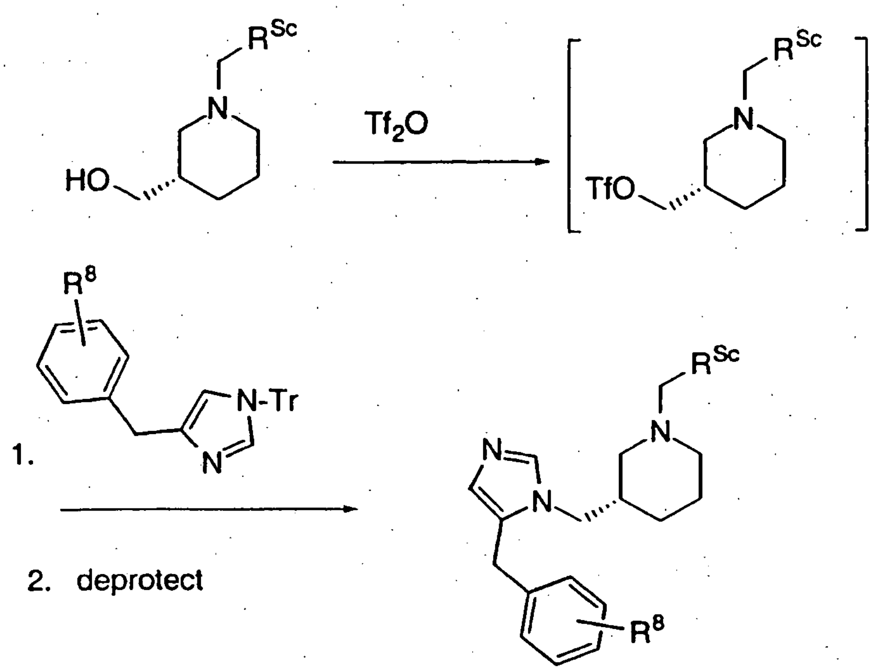


SCHEME 67

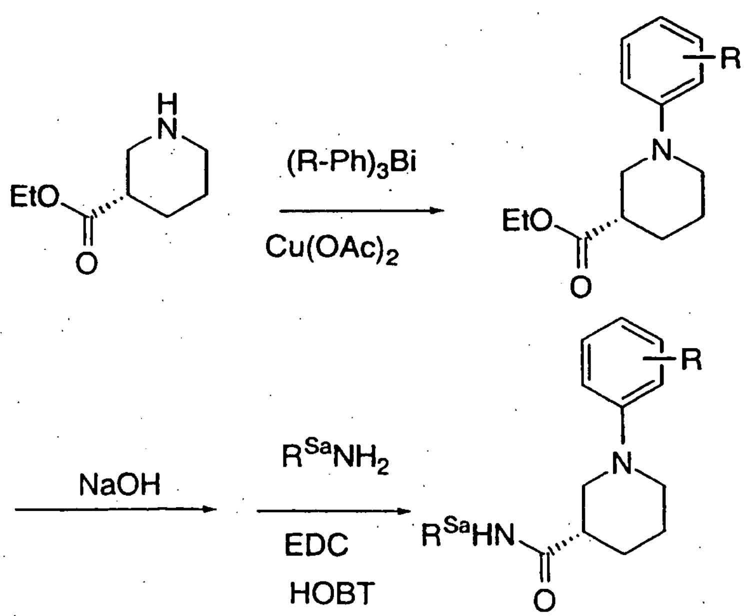


R^Sc
HO
N
pyridine·SO3
H
O
16
R^SaNH2
Na(Ac)3BH
or
NaCNBH3
H
R^Sa
20
RSO2X
RCHO
Na(OAc)3BH
RCX
RO2S
RCH2
R

SCHEME 68



SCHEME 69



In the above Schemes 62-69 it is understood that

$$R^{Sa} \text{ and } R^{Sd} \text{ are } \overset{\displaystyle (R^4)_r}{\overset{|}{V}} - A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n \left(\overset{\displaystyle R^5}{\overset{|}{W}} \right)_t - (CR^{1b}{}_2)_p -\S$$

or a protected precursor thereof;

$R^{Sc}CH_2$- is R^2 or a protected precursor thereof;
R^{Sb}- is R^6 or a protected precusor thereof; and
R- is a "substituent" or a protected precusor thereof.

It is understood that a variety of amines and acids, either commercially available or readily synthesized by reactions well known in the art, which contain the side-chain moieties R^{Sa} and $R^{Sd}(C{=}O)$ may be utilized in the reactions described hereinabove.

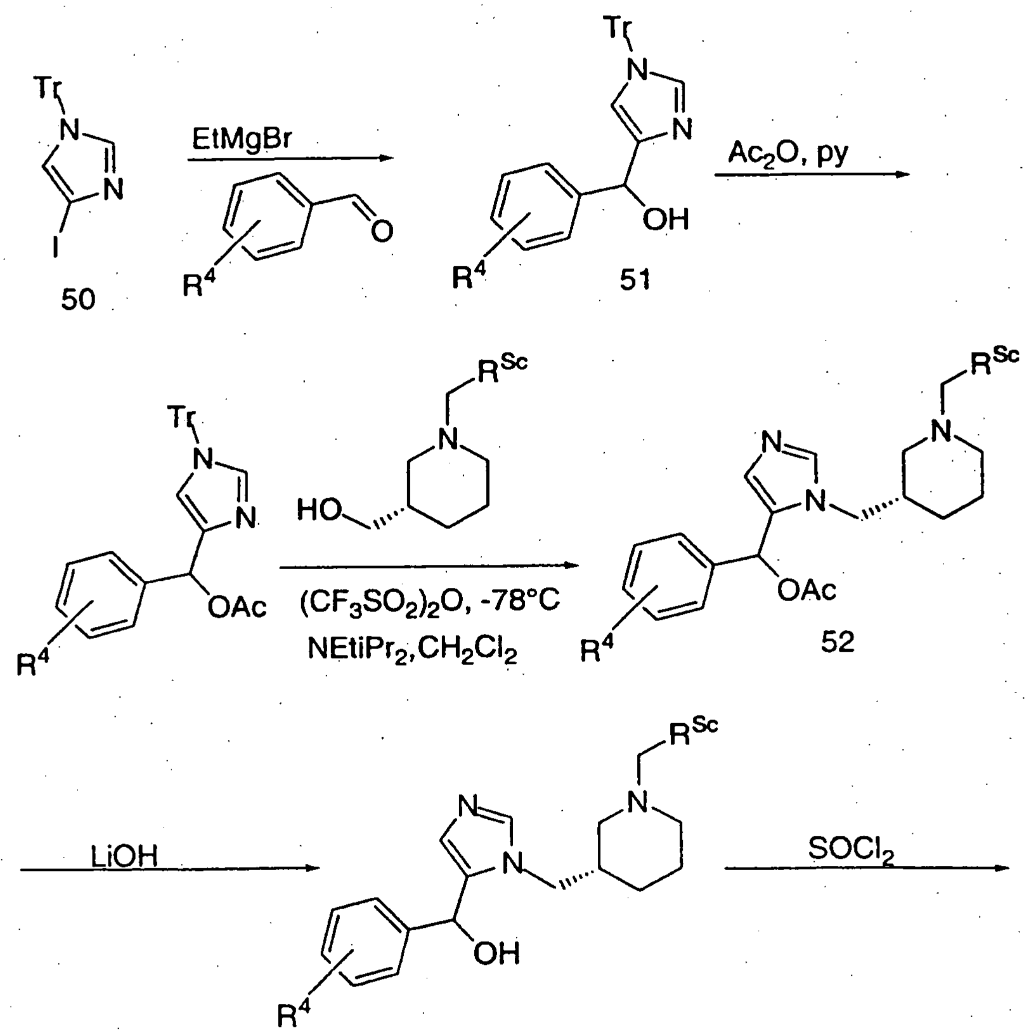
Compounds of the instant invention wherein the $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 70. Thus, the N-protected imidazolyl iodide **50** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **51**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 68) provides the instant compound **52**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

Scheme 71 illustrates synthesis of an instant compound wherein a non-hydrogen R^{5b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **53** may be selectively iodinated to provide the 5-iodoimidazole **54**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **55**. Intermediate **55** can then undergo the alkylation reactions that were described hereinabove.

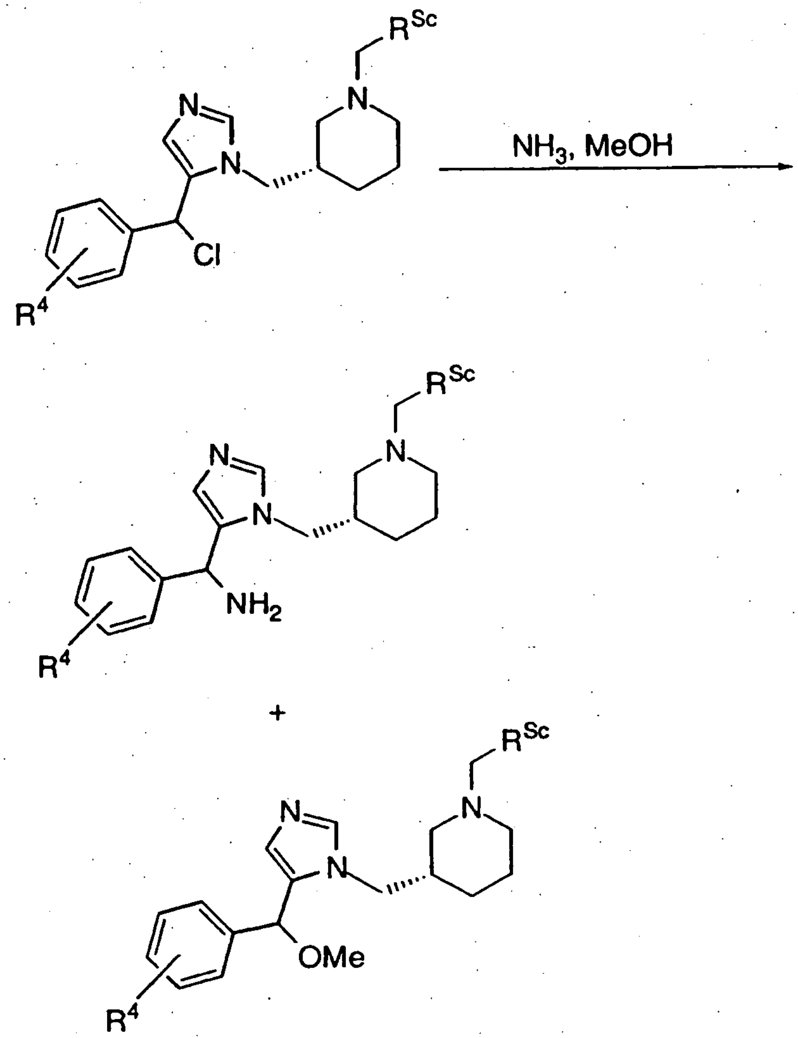
Compounds of the instant invention wherein the $A^1(CR^1{}_2)_nA^2(CR^1{}_2)_n$ linker is oxygen may be synthesized by

methods known in the art, for example as shown in Scheme 72. The suitably substituted phenol **56** may be reacted with methyl N-(cyano) methanimidate to provide the 4-phenoxyimidazole **57**. After selective protection of one of the imidazolyl nitrogens, the intermediate **58** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

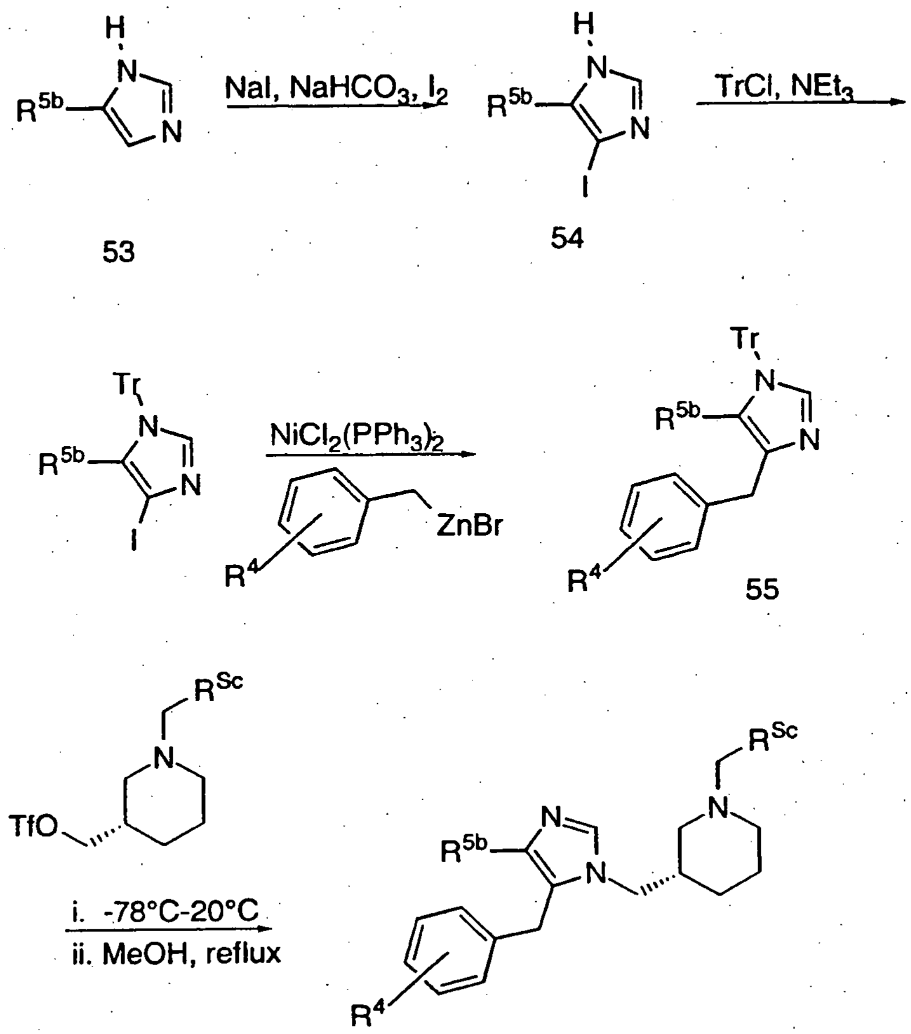
Scheme 70



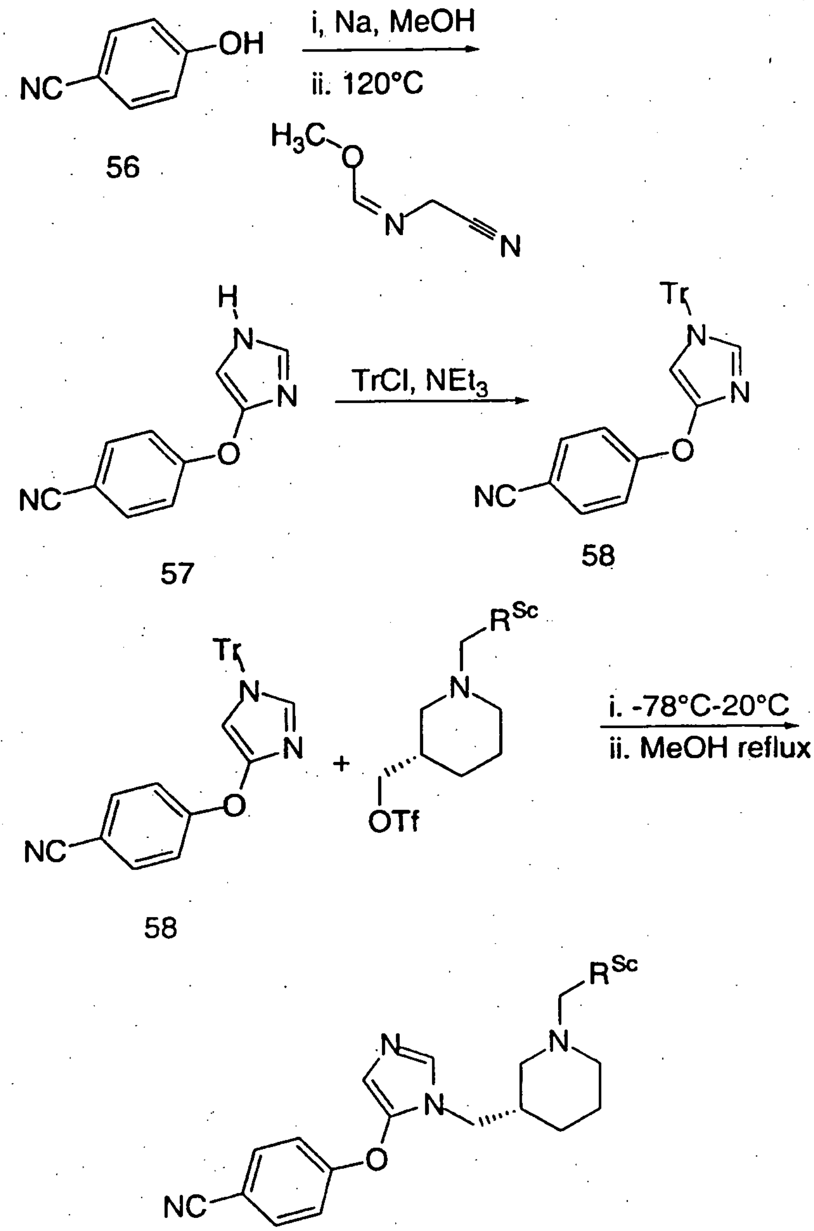
SCHEME 70 (continued)



SCHEME 71



SCHEME 72



The compounds of the formula (IV) are prepared by employing reactions as shown in the Schemes 73-94, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting

groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a, R^b and R^{sub}, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5, and substituents on Z^1 and Z^2; however their point of attachment to the ring is illustrative only and is not meant to be limiting. The compounds referred to in the Synopsis of Schemes 73-94 by Roman numerals are numbered starting sequentially with I and ending with XLVI.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 73-94:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. In Scheme 73, for example, the synthesis of macrocyclic compounds of the instant invention containing suitably substituted piperazines and the preferred benzylimidazolyl moiety is outlined. Preparation of the substituted piperazine intermediate is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., **1990**, *22*, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride , chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which may then be deprotected by catalytic reduction to provide intermediate V. Intermediate V may then be coupled to intermediate VII, prepared from 4-imidazolylacetic acid VI in several step as

illustrated. Once the amide bond is formed to yield the intermediate VIII, cesium carbonate nucleophilic aromatic substitution reaction conditions result in an intramolecular cyclization to yield compound IX of the instant invention. This cyclization reaction depends on the presence of an electronic withdrawing moiety (such as nitro, cyano, and the like) either ortho or para to the fluorine atom.

Scheme 74 illustrates the synthesis of instant compounds wherein an amido bond is formed between the piperazine nitrogen and the linker to the Y group. Thus, the protected piperazine X is coupled to a naphthoic acid having a suitably positioned benzyloxy moiety. Consecutive removal of the Boc and benzyl protecting groups provided intermediate XI, which may be coupled to a suitably substituted 1-benzylimidazole aldehyde XII to give intermediate XIII. Intramolecular cyclization takes place as previously described using the cesium carbonate conditions to provide instant compound XIV.

Scheme 75 illustrates the preparation of instant compounds which incorporate a piperazinone moiety in the macrocyclic ring. Thus the suitably substituted benzyloxybenzyl mesylate XV is reacted with a 4-protected 2-piperazinone XVI to provide the 1-benzyl-2-piperazinone intermediate XVII. Intermediate XVII is doubly deprotected in the presence of Boc anhydride to provide the N-Boc protected piperazinone, which is deprotected to give intermediate XVIII. Reductive N-alkylation of intermediate XVIII with a suitably substituted 1-benzylimidazole aldehyde XII provides intermediate XIX, which can undergo intramolecular cyclization under the cesium carbonate conditions to give compound XX of the instant invention.

Synthesis of compounds of the invention characterized by direct attachment of an aryl moiety to the piperazinone moiety and incorporation of a third aromatic carbocyclic moiety into the macrocycle is illustrated in Scheme 76. A benzyloxyphenoxyanaline XIII, prepared in three steps from a suitably substituted 2-benzyloxyphenol XXI and a suitably substituted nitrochlorobenzene XXII, is reacted with chloroacetyl chloride to provide intermediate XXIV. Intermediate XXIV is reacted with a suitably substituted ethanolamine

and the resulting amido alcohol cyclized to form the piperazinone moiety of intermediate XXV. Intermediate XXV is reductively alkylated as described in Schemes 74 and 75 to provide intermediate XXVI. Deprotection, followed by intramolecular cyclization provides compound XXVII of the instant invention.

Scheme 77 illustrates expansion of the macrocyclic ring to a "18-membered" system by utilizing a suitably substituted 3-benzyloxyphenol XXVIII in the place of the 2-benzyloxyphenol XXI. Scheme 77 also illustrates the use of a reduced amino acid (such as methioninol) to provide substitution specifically at the 5-position of the piperazinone moiety.

Scheme 78 illustrates that the synthetic strategy of building the piperazinone onto a alcoholic aromatic amine can also be utilized to prepare compounds of the instant invention wherein a naphthyl group forms part of the macrocyclic backbone.

Scheme 79 illustrates the synthetic strategy that is employed when the R^8 substitutent is not an electronic withdrawing moiety either ortho or para to the fluorine atom. In the absence of the electronic withdrawing moiety, the intramolecular cyclization can be accomplished via an Ullmann reaction. Thus, the imidazolylmethylacetate XXXII is treated with a suitably substituted halobenzylbromide to provide the 1-benzylimidazolyl intermediate XXXIII. The acetate functionality of intermediate XXXIII was converted to an aldehyde which was then reductively coupled to intermediate XVIII, prepared as illustrated in Scheme 75. Coupling under standard Ullmann conditions provided compound XXXIV of the instant invention.

Illustrative examples of the preparation of compounds of the instant invention that incorporate a 2,5-diketopiperazine moiety and a 2,3-diketopiperazine moiety are shown in Schemes 80-81 and Schemes 82-83 respectively.

Scheme 84 illustrates the manipulation of a functional group on a side chain of an intermediate 2,5-diketopiperazine. The side chain of intermediate IIIa, obtained as illustrated in Scheme 73

from protected aspartic acid, may be comprehensively reduced and reprotected to afford intermediate XXXV, which can deprotected or can be alkylated first followed by deprotection to provide intermediate IVa having an ether sidechain. The intermediate IVa can be incorporated into the reaction sequence illustrated in Scheme 73.

Scheme 85 illustrates direct preparation of a symmetrically substituted piperazine intermediate from a suitably substituted analine (such as intermediate XXIII from Scheme 76) and a suitably substituted *bis*-(chloroethyl)amine XXXVII. The intermediate XXXVIII can be utilized in the reaction sequence illustrated in Scheme 73 to produce compound IXL of the instant invention

Preparation of a substituted piperazinone intermediate XVIIIa starting from a readily available N-protected amino acid XL is illustrated in Scheme 86.

Scheme 87 illustrates preparation of an intermediate piperazinone compound XLI having a substituent at the 3-position that is derived from the starting protected amino acid XL.

Incorporation of a spirocyclic moiety (for example, when R^2 and R^3 are combined to form a ring) is illustrated in Scheme 88.

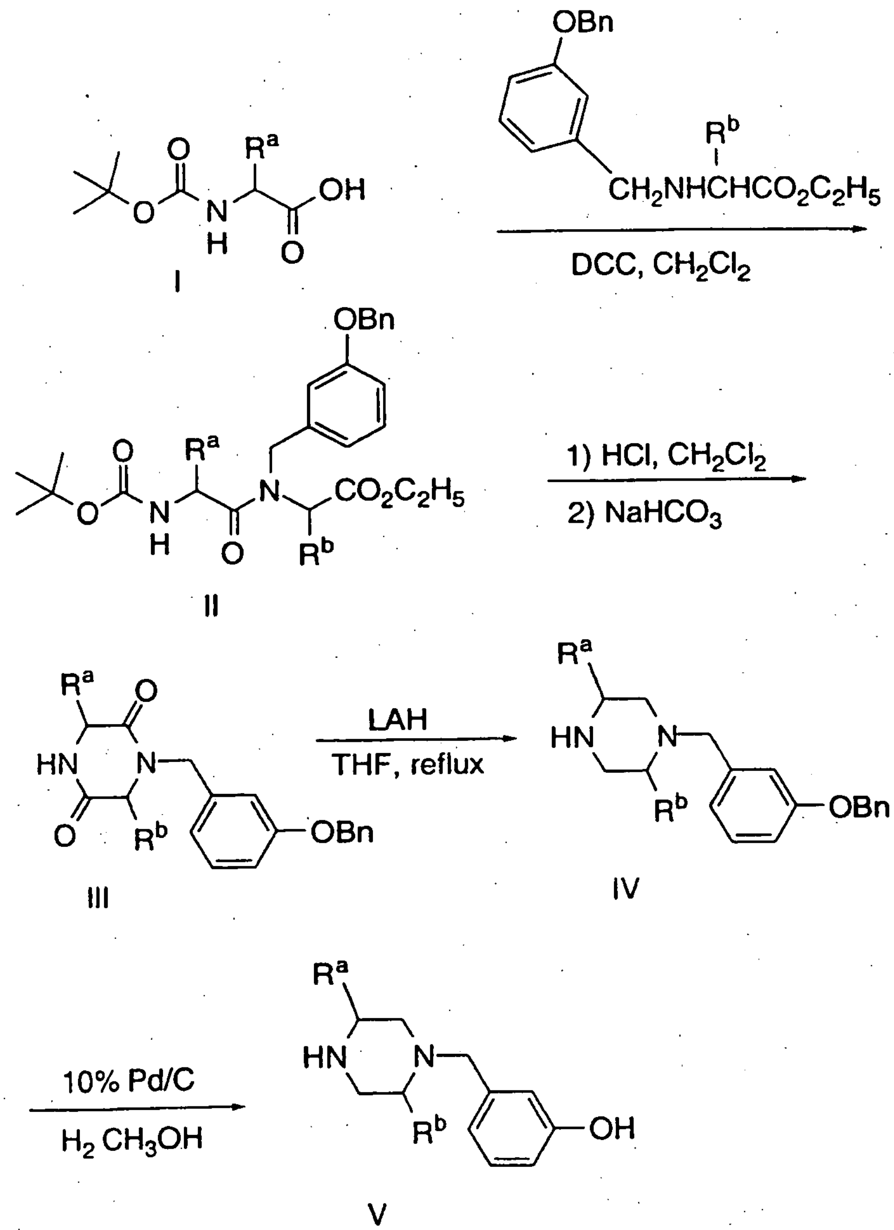
Scheme 89 illustrates the use of an optionally substituted homoserine lactone XLII to prepare a Boc-protected piperazinone XLIII. Intermediate XLIII may be deprotected and reductively alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of intermediate XLIII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate XLIV. Intermediate XLIII may also be oxidized to provide the carboxylic acid on intermediate XLV, which can be utilized form an ester or amide moiety.

Amino acids of the general formula XL which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 90 starting with the readily prepared imine XLVI.

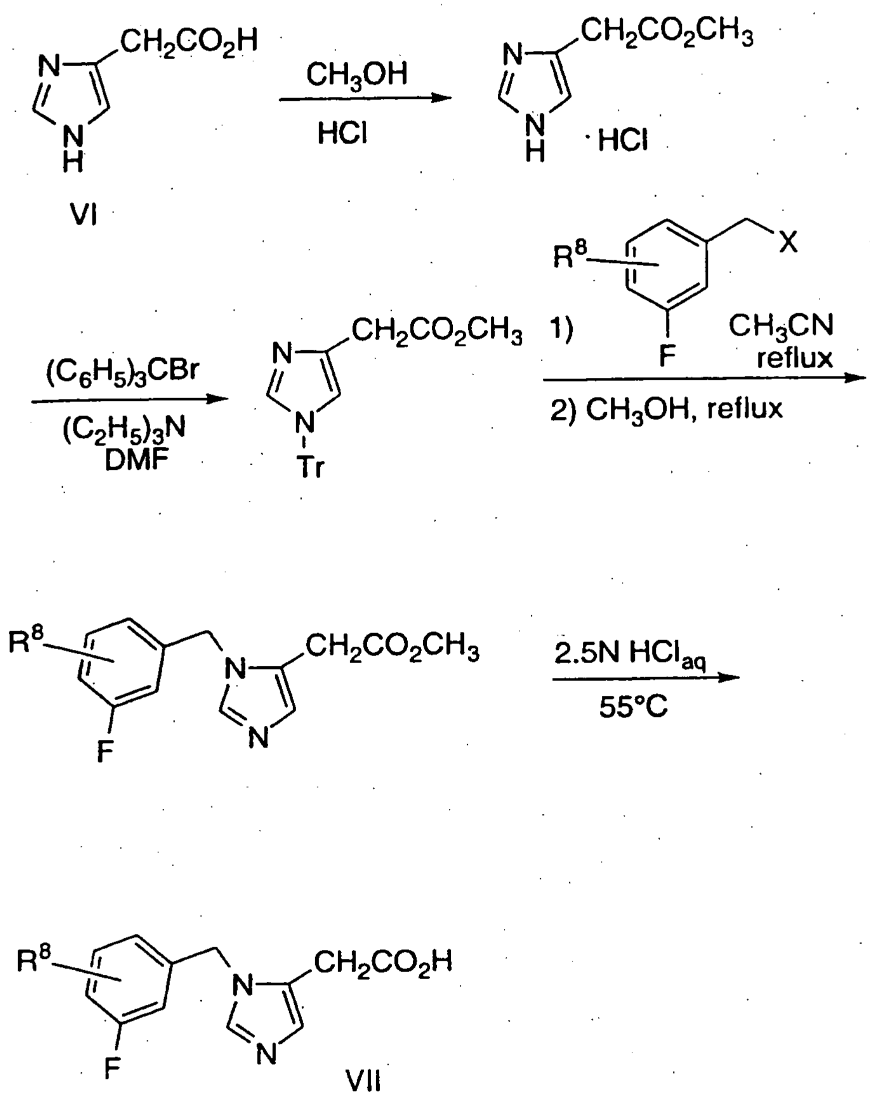
Schemes 91-94 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the

variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

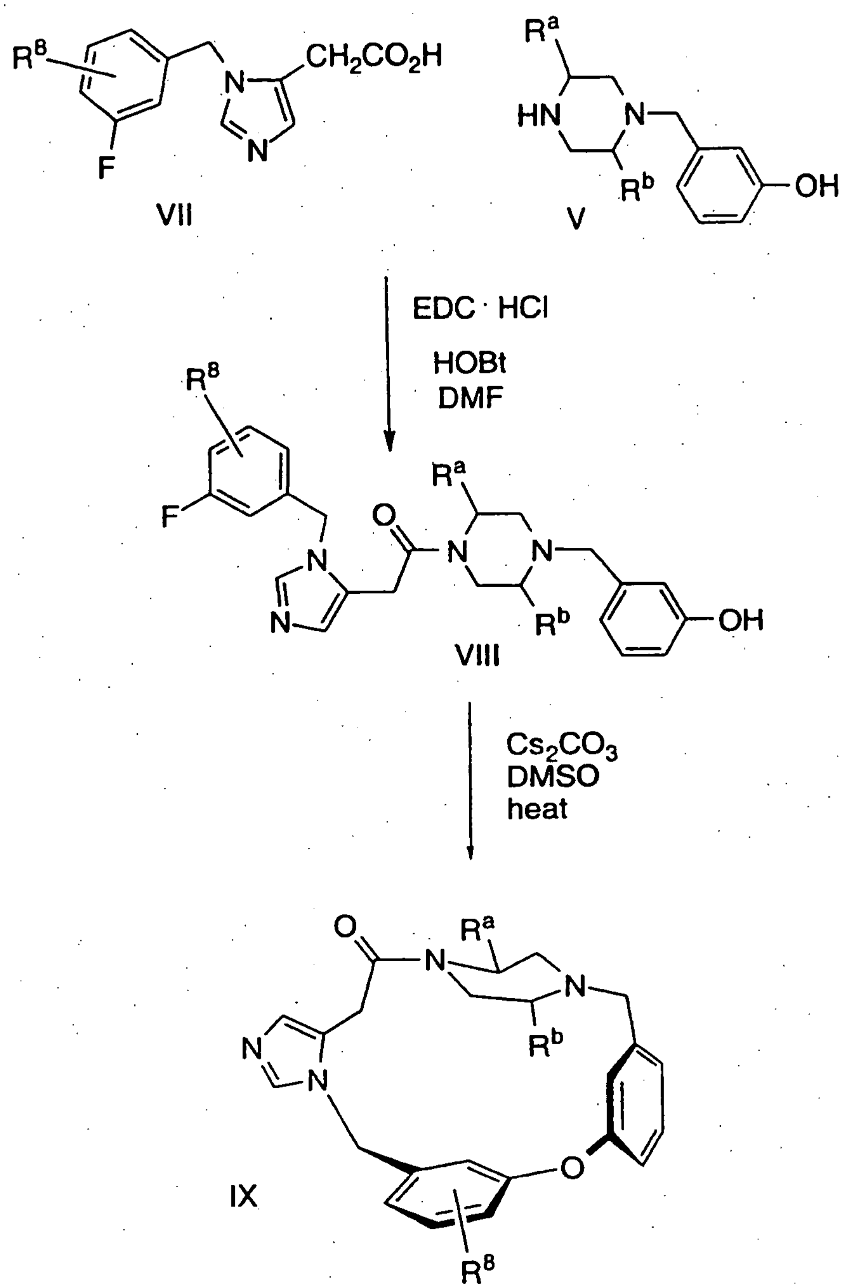
SCHEME 73



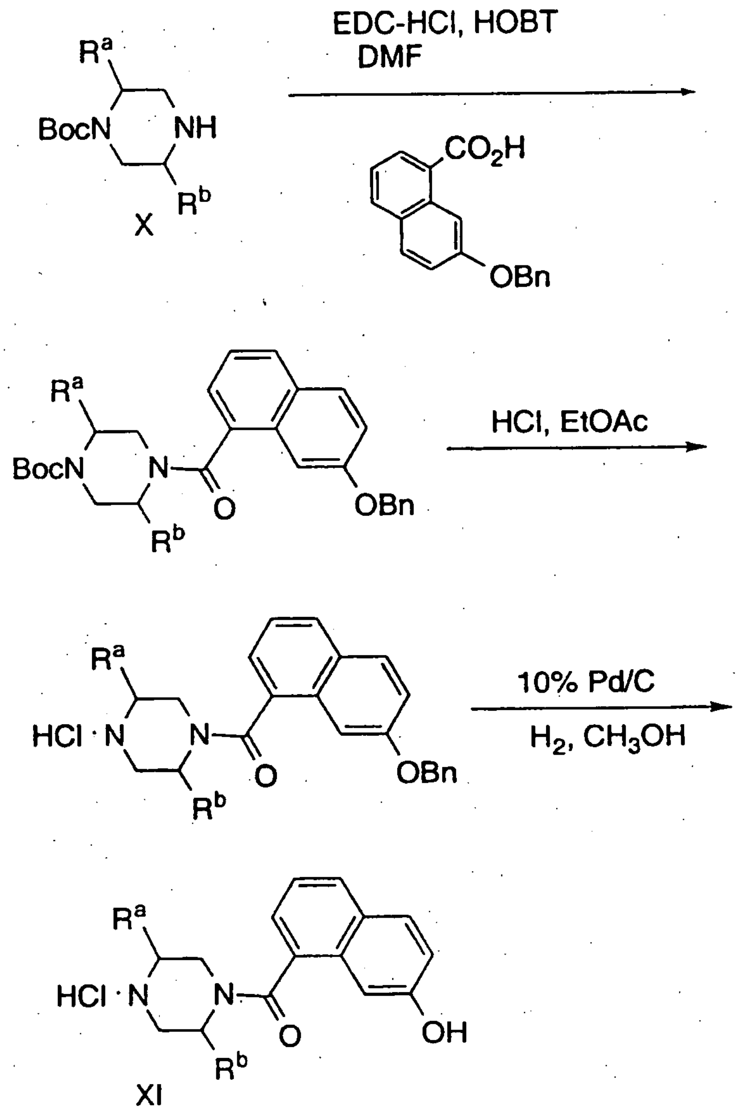
SCHEME 73 (continued)



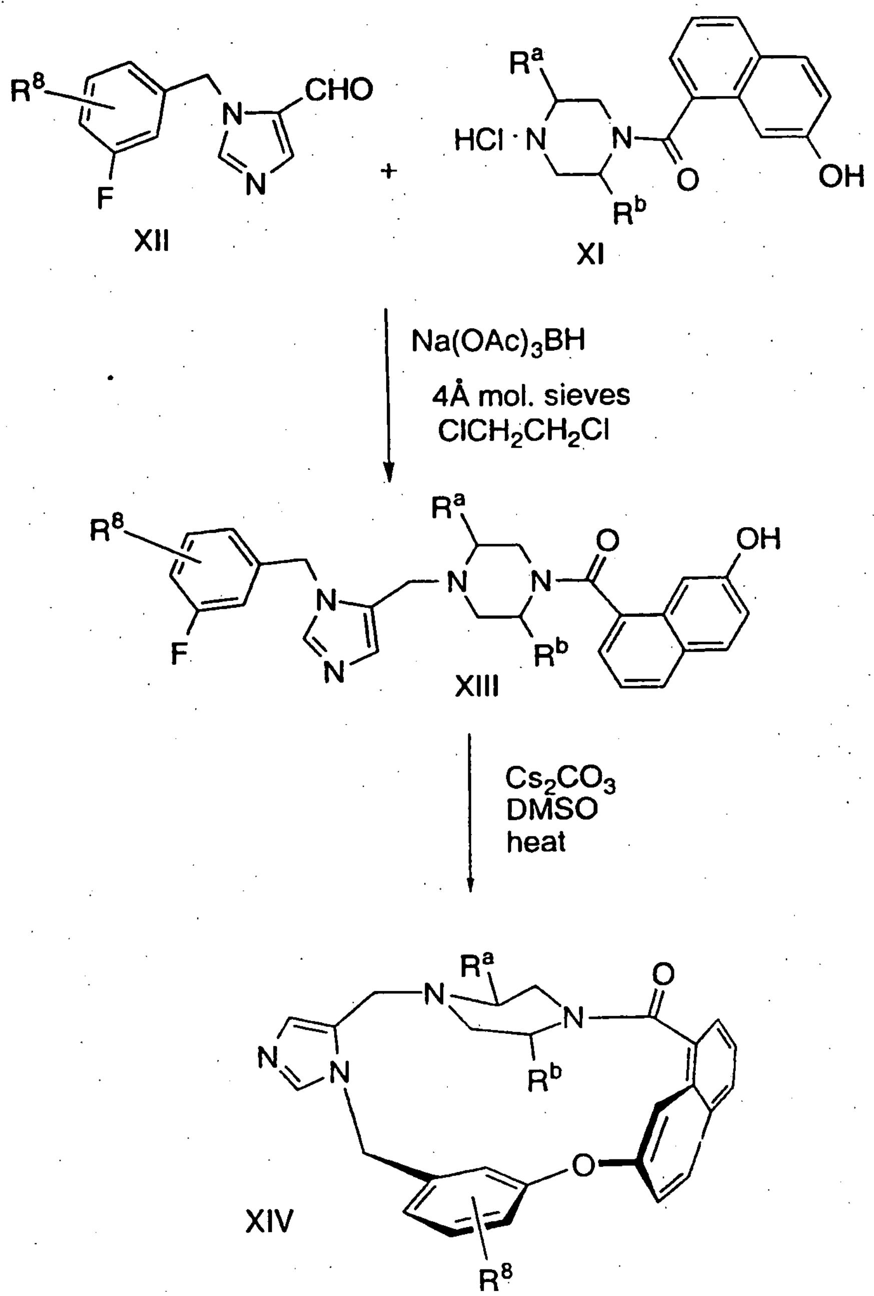
SCHEME 73 (continued)



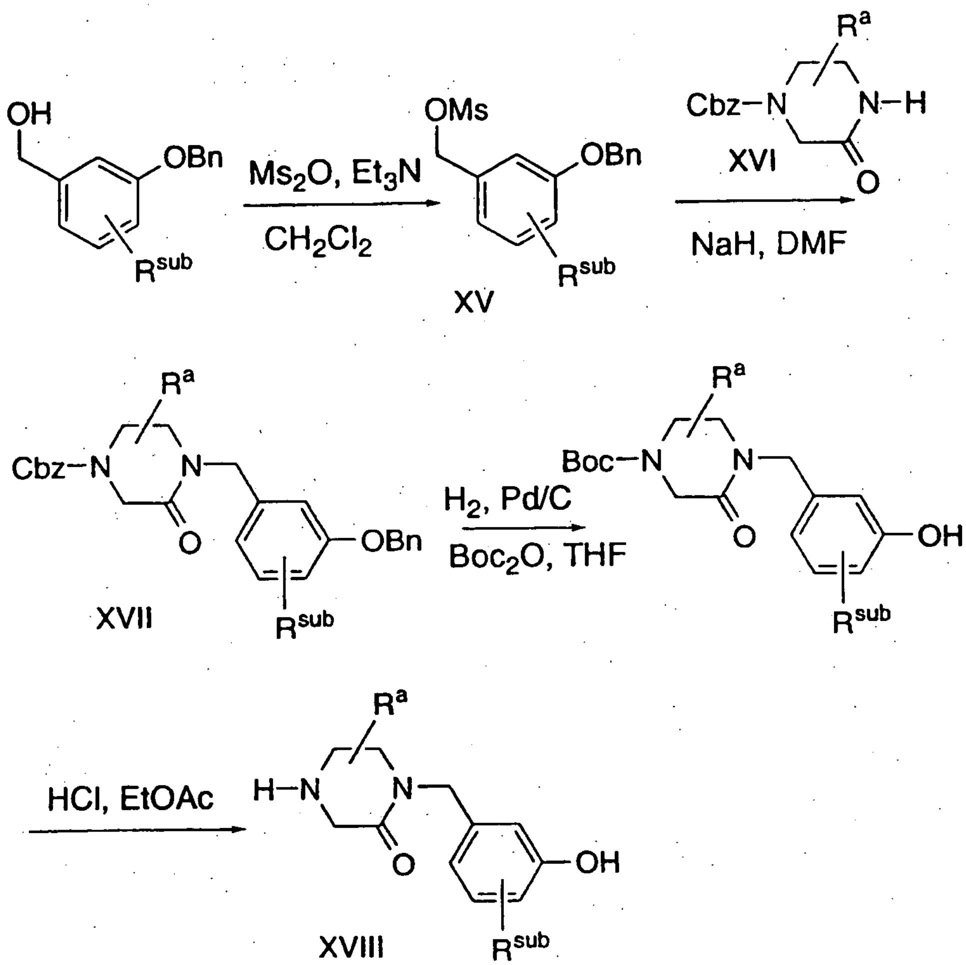
SCHEME 74



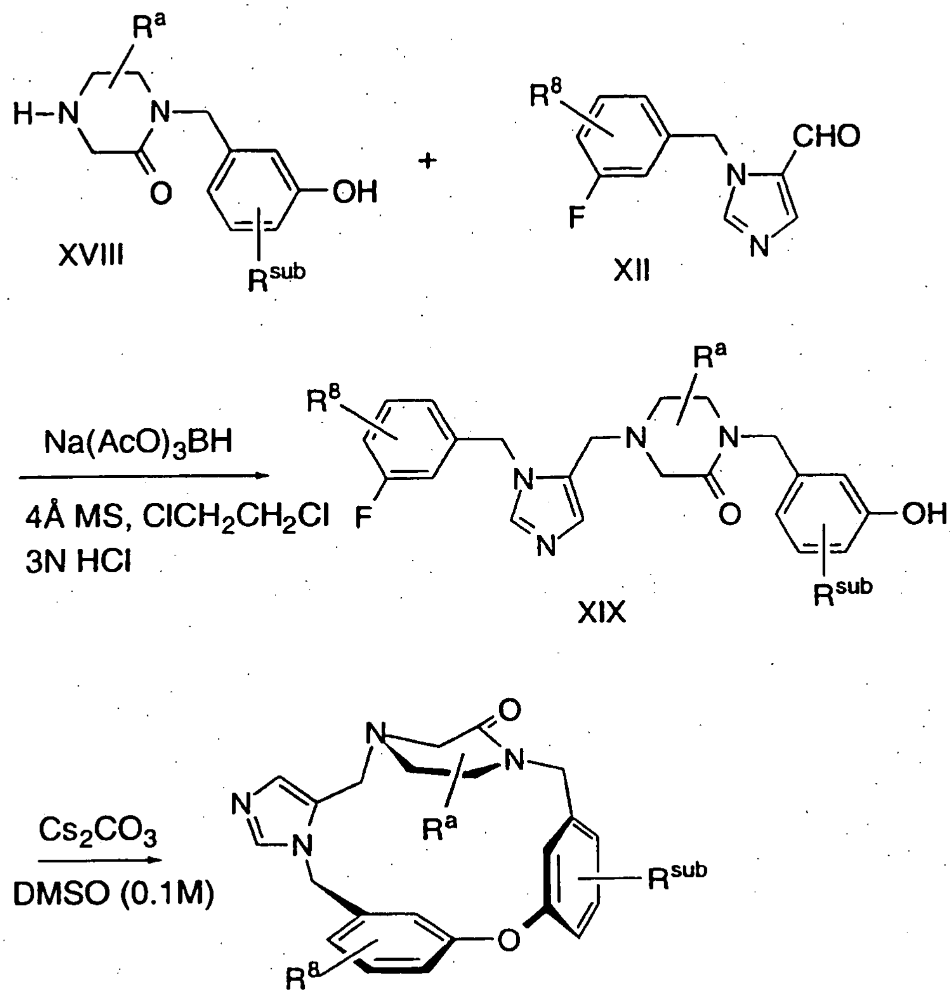
SCHEME 74 (continued)



SCHEME 75

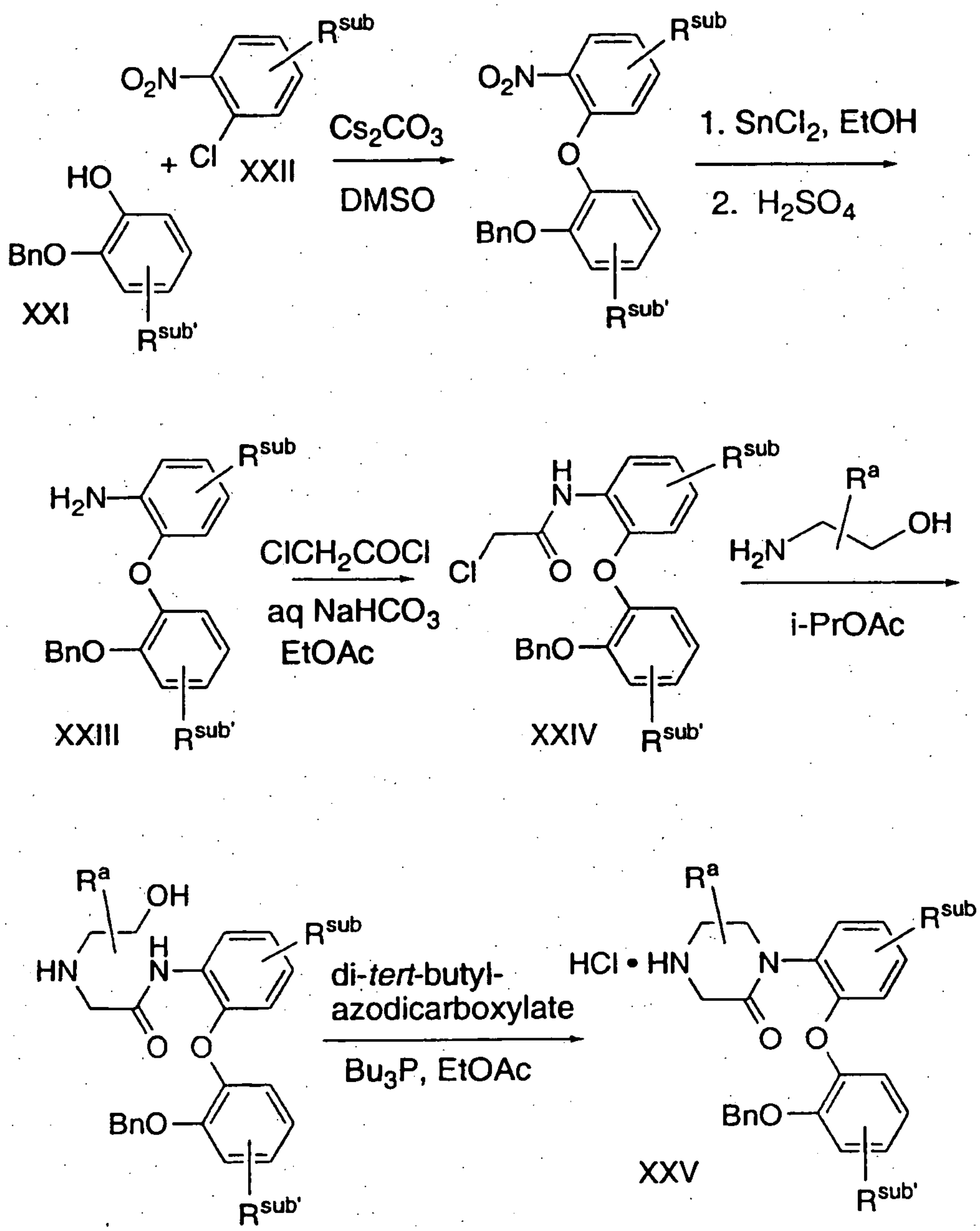

OH
OBn
Rsub
Ms2O, Et3N
CH2Cl2
OMs
OBn
Rsub
XV
Ra
Cbz–N
N–H
O
XVI
NaH, DMF
Ra
Cbz–N
N
O
OBn
Rsub
XVII
H2, Pd/C
Boc2O, THF
Ra
Boc–N
N
O
OH
Rsub
HCl, EtOAc
Ra
H–N
N
O
OH
Rsub
XVIII

SCHEME 75 (continued)



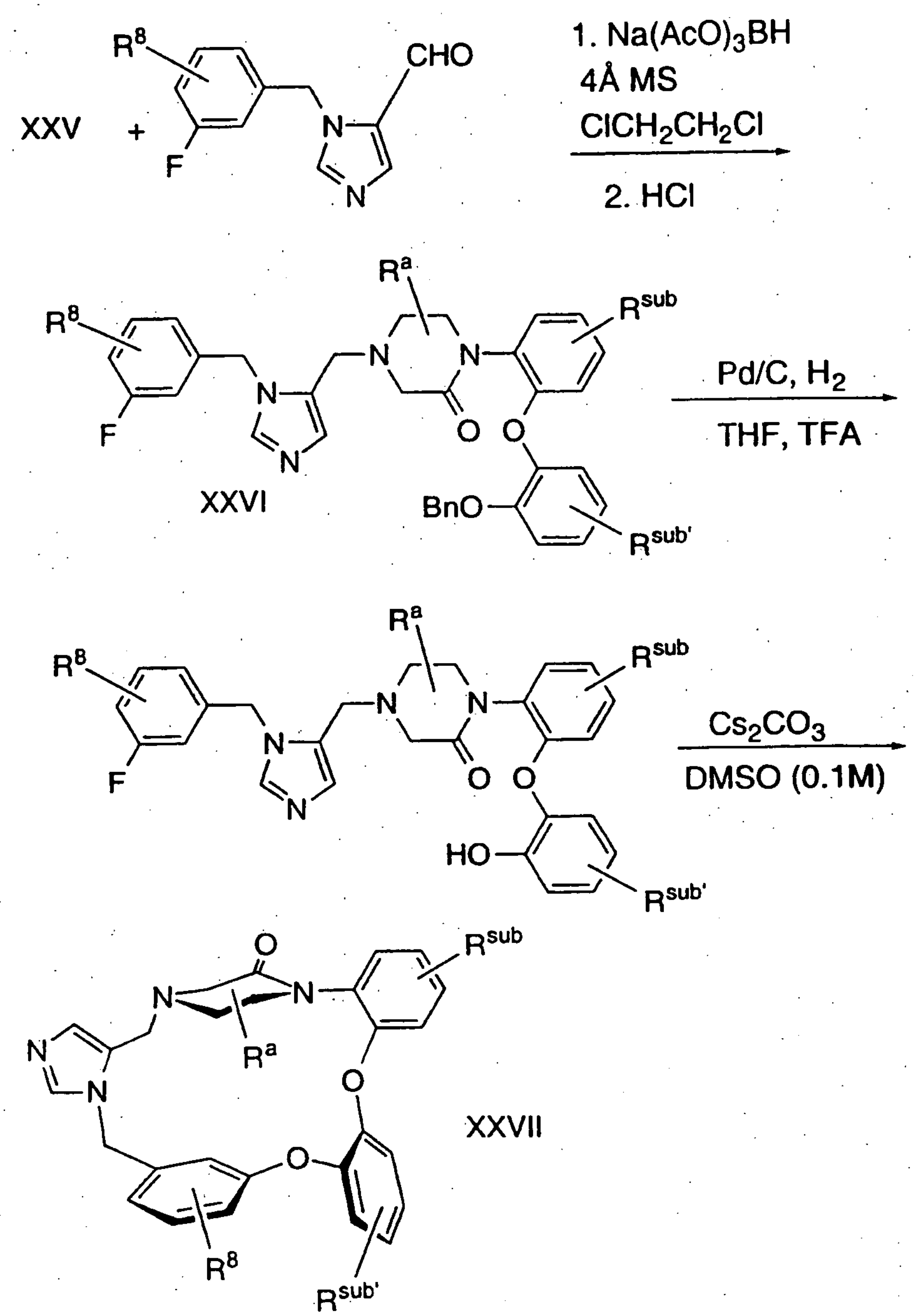
XVIII XII XIX XX

SCHEME 76

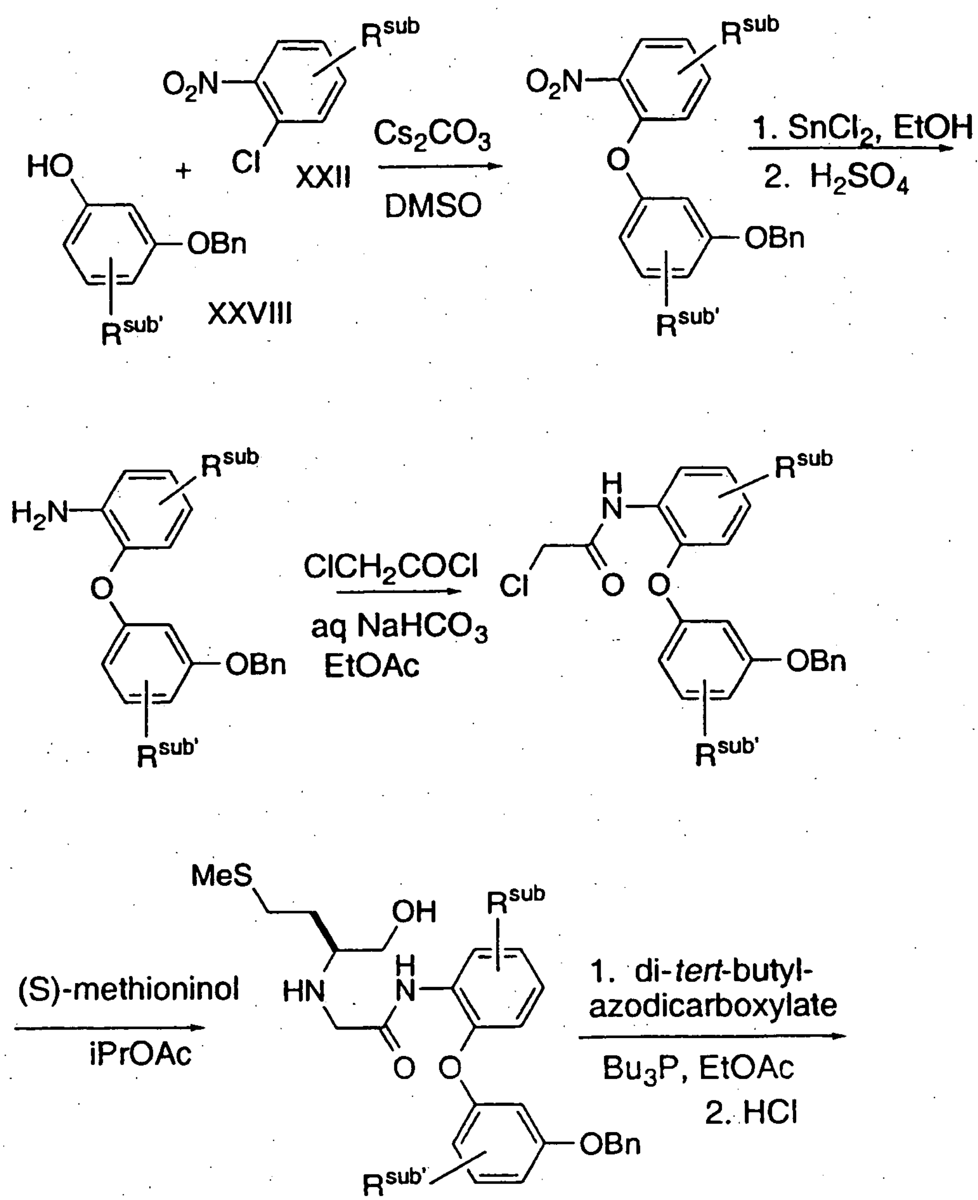


R^sub
O2N
Cl
XXII
HO
BnO
XXI
R^sub'
Cs2CO3
DMSO
1. SnCl2, EtOH
2. H2SO4
H2N
XXIII
ClCH2COCl
aq NaHCO3
EtOAc
XXIV
R^a
H2N
OH
i-PrOAc
HN
di-tert-butyl-
azodicarboxylate
Bu3P, EtOAc
HCl • HN
XXV

SCHEME 76 (continued)

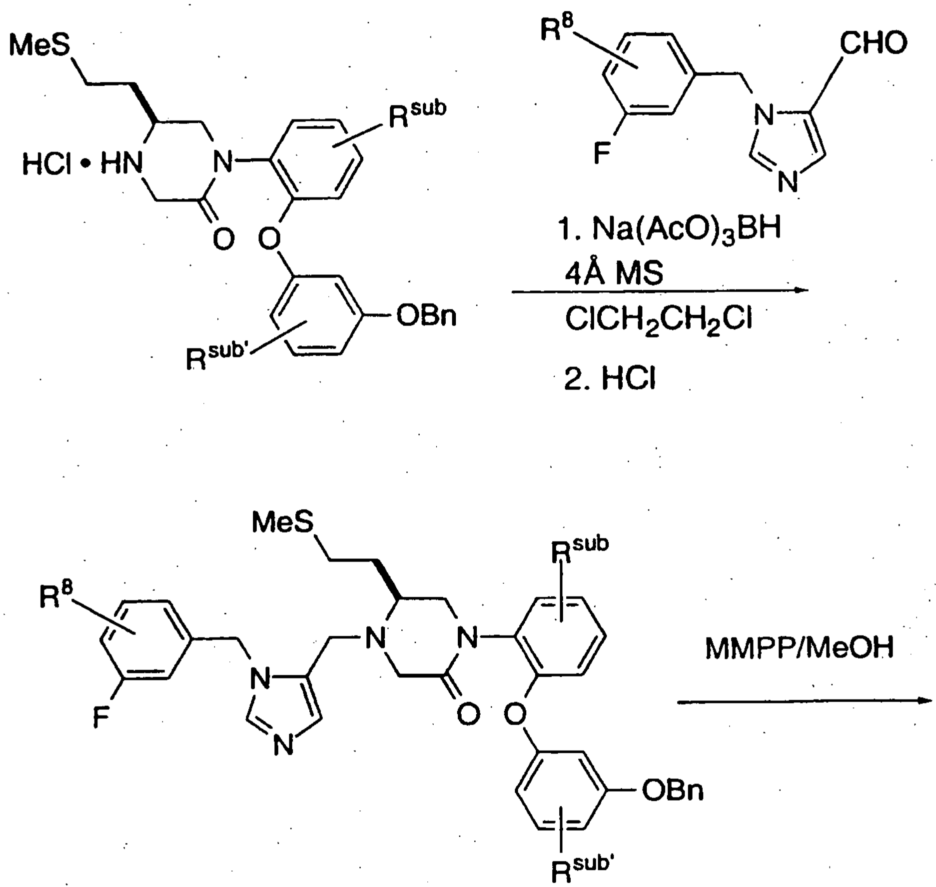


SCHEME 77

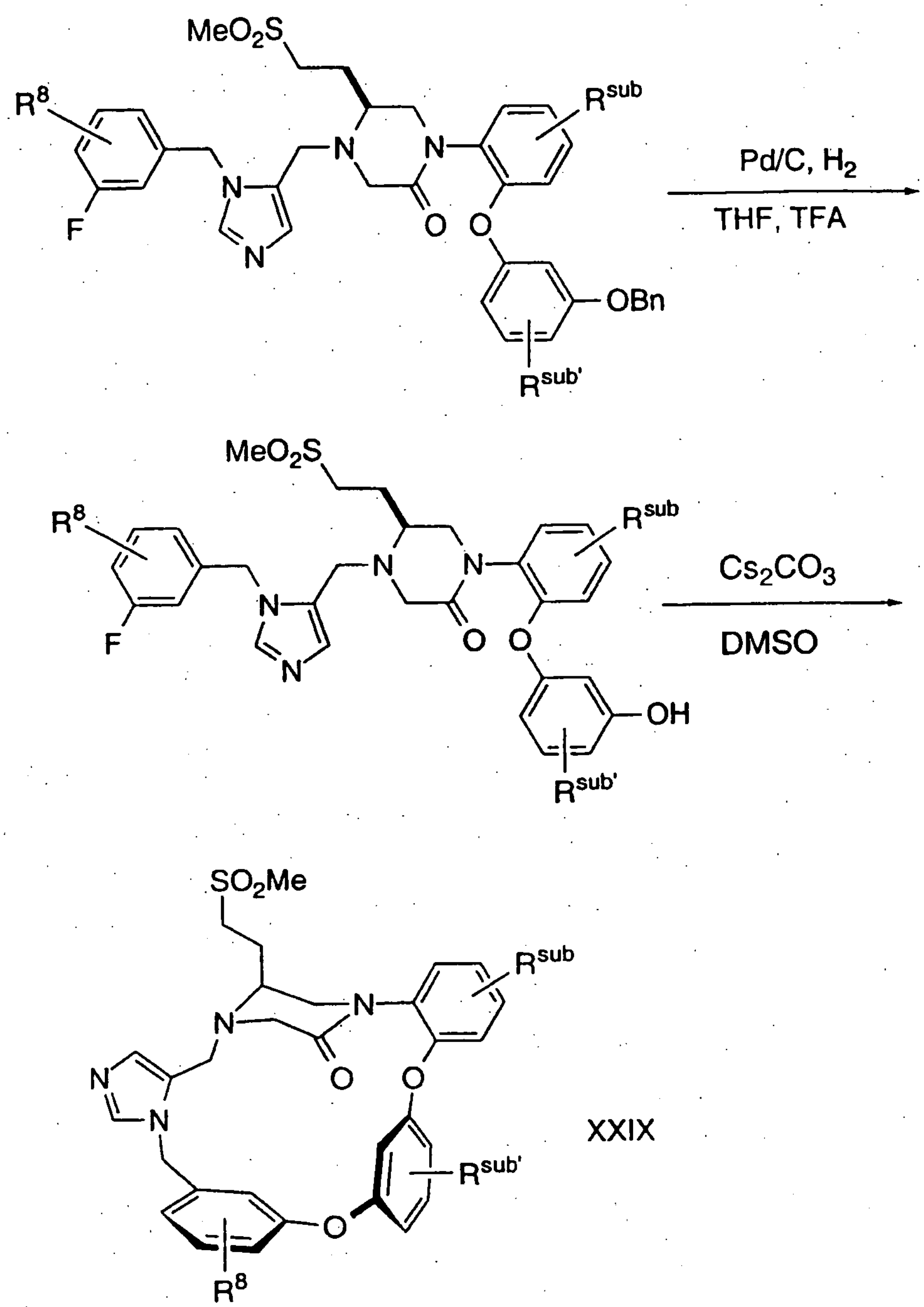


HO
OBn
$R^{sub'}$
XXVIII
+
O_2N
Cl
R^{sub}
XXII
Cs_2CO_3
DMSO
1. $SnCl_2$, EtOH
2. H_2SO_4
H_2N
$ClCH_2COCl$
aq $NaHCO_3$
EtOAc
(S)-methioninol
iPrOAc
MeS
OH
HN
1. di-*tert*-butyl-azodicarboxylate
Bu_3P, EtOAc
2. HCl

SCHEME 77 (continued)

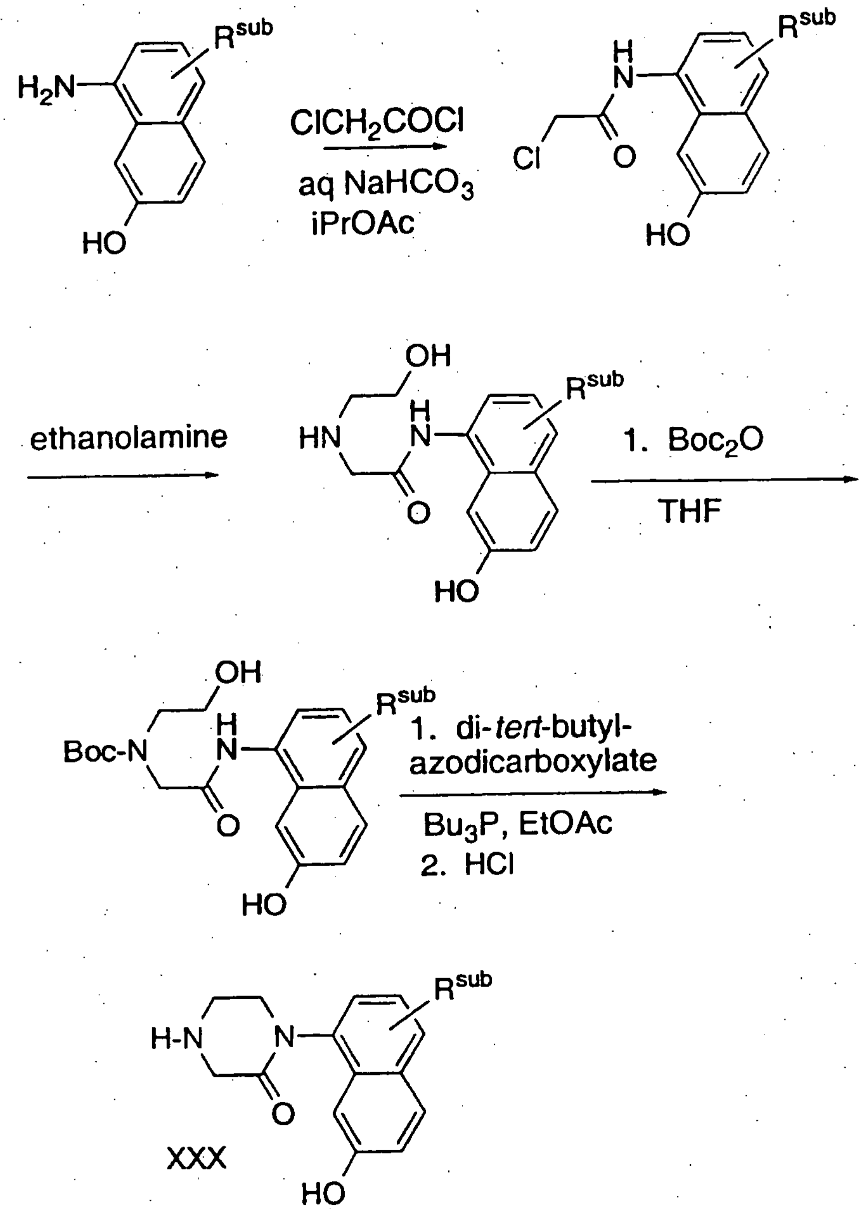


SCHEME 77 (continued)



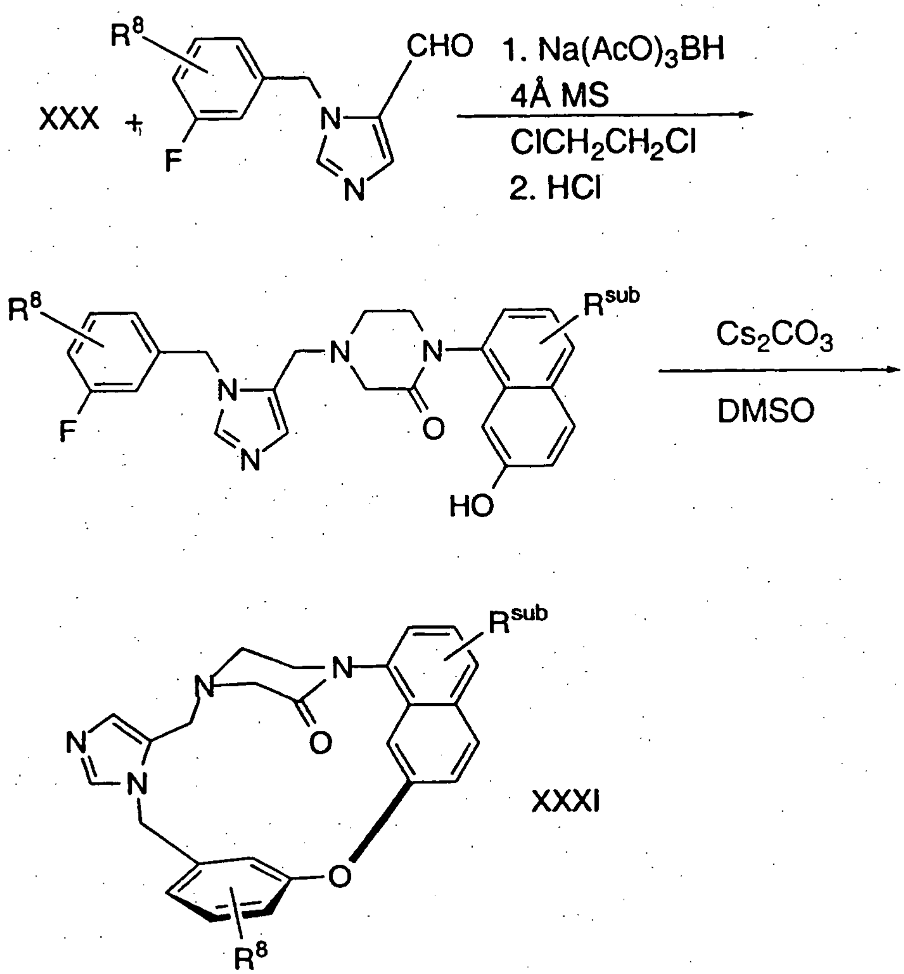
XXIX

SCHEME 78



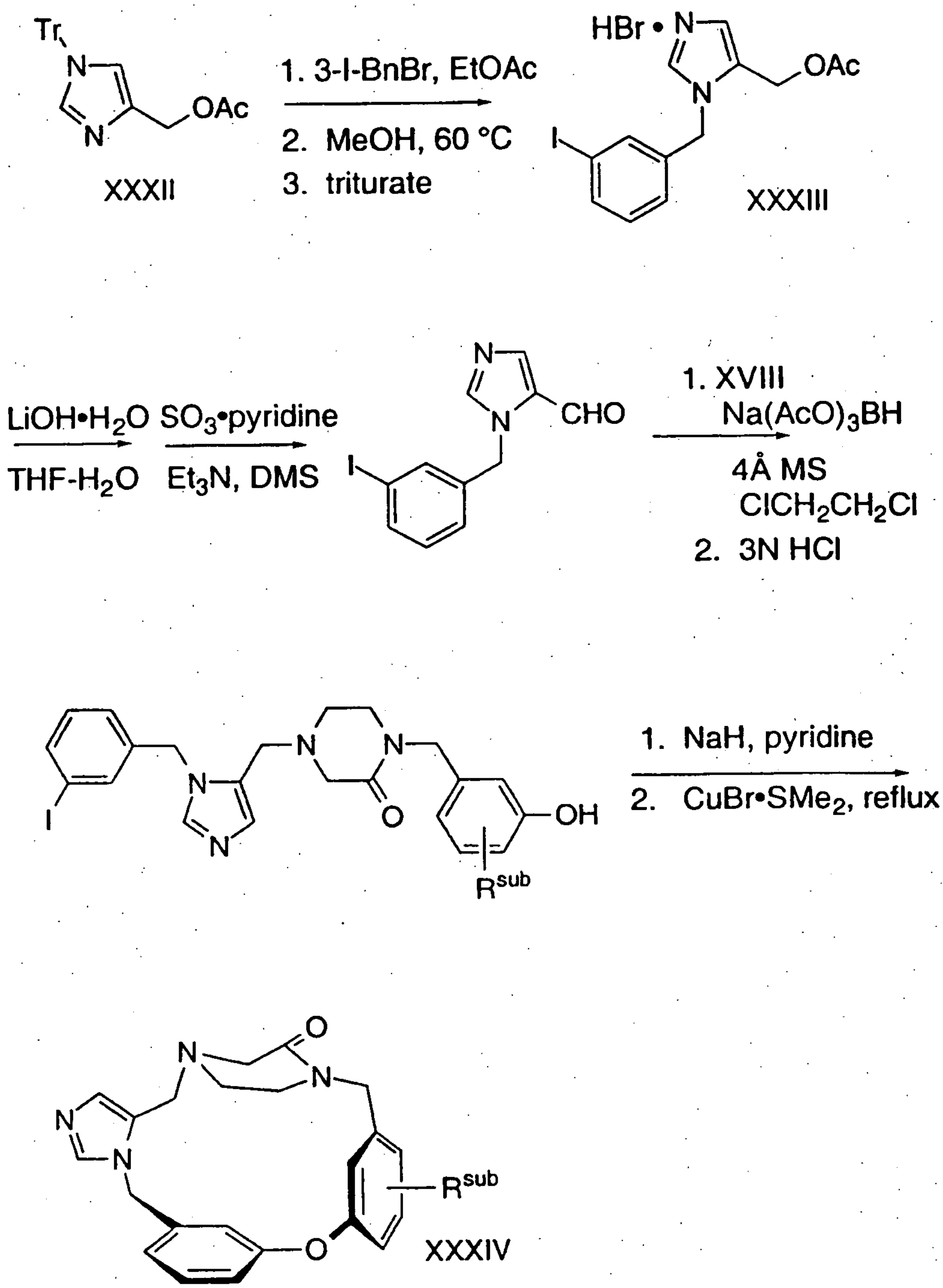
XXX

SCHEME 78 (continued)

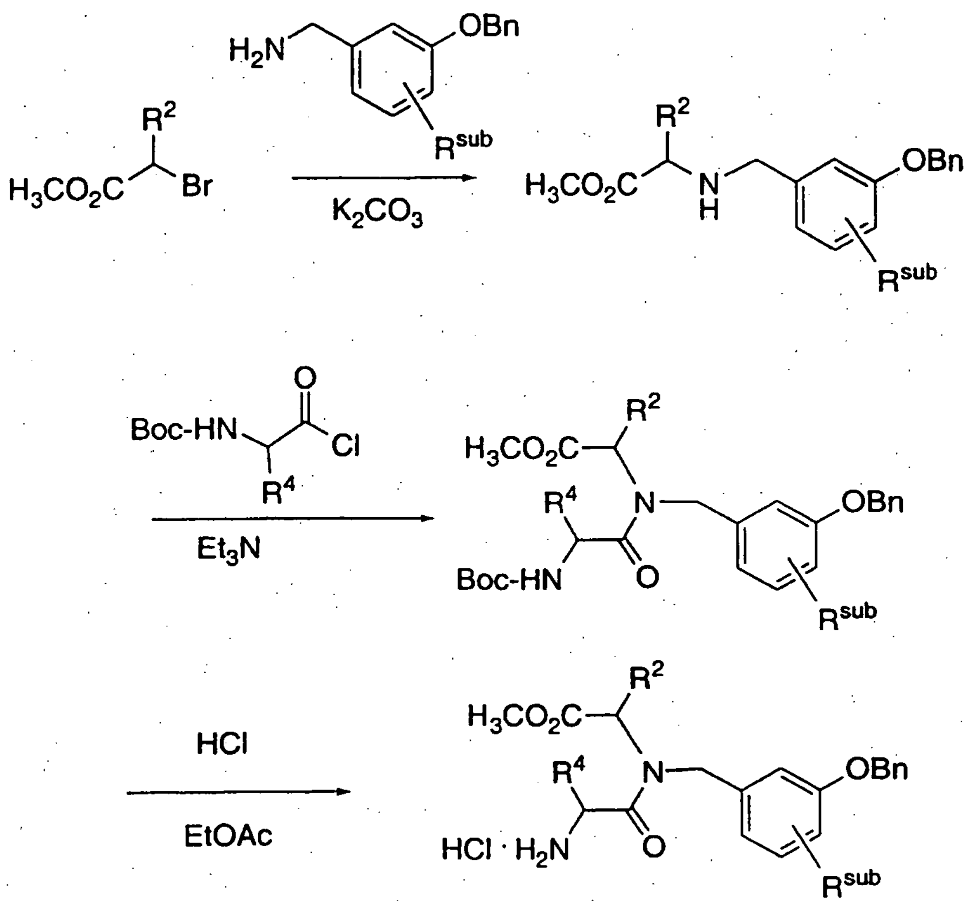


XXXI

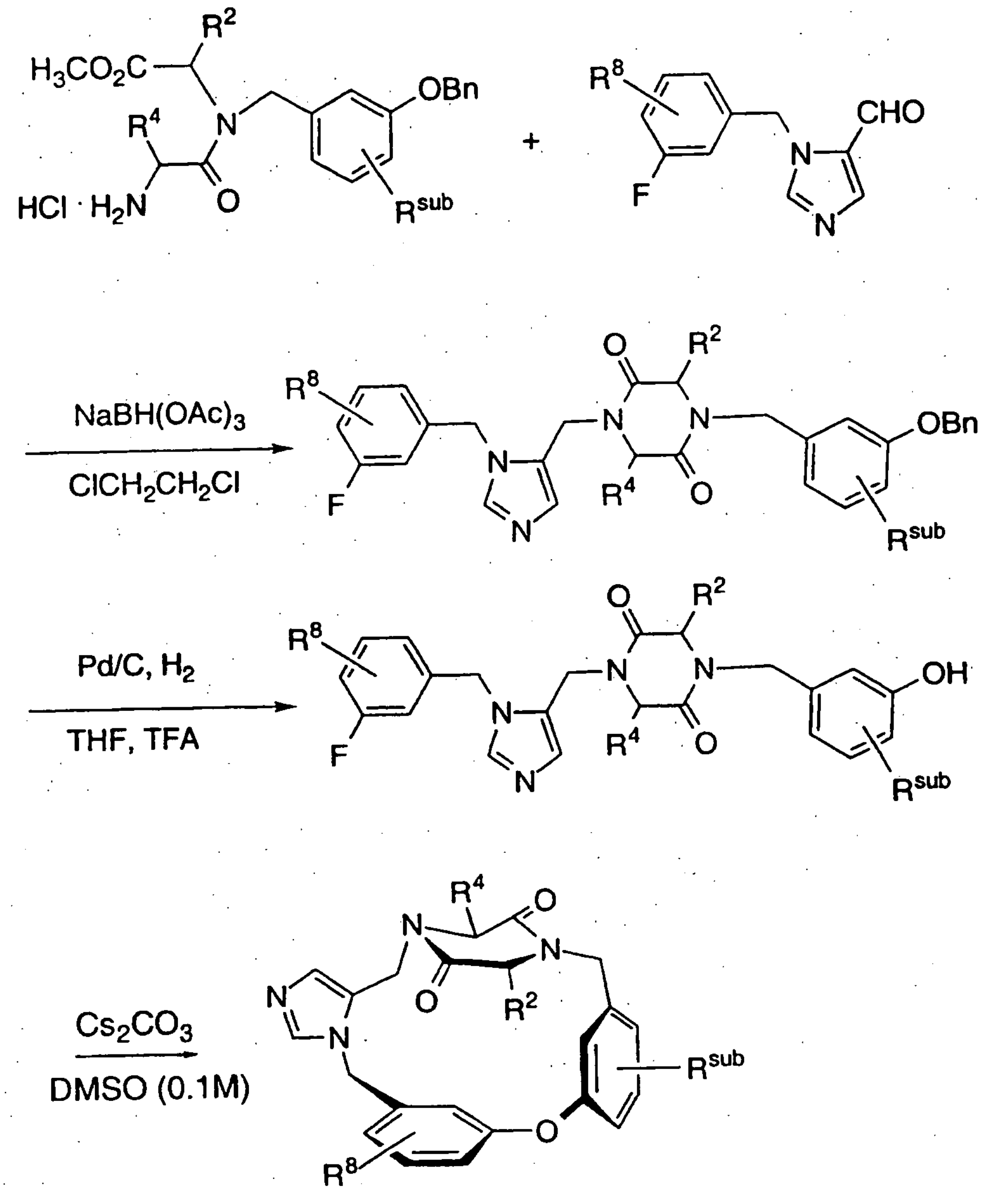
SCHEME 79


Tr
OAc
XXXII
1. 3-I-BnBr, EtOAc
2. MeOH, 60 °C
3. triturate
HBr • N
OAc
I
XXXIII
LiOH•H2O
THF-H2O
SO3•pyridine
Et3N, DMS
CHO
I
1. XVIII
Na(AcO)3BH
4Å MS
ClCH2CH2Cl
2. 3N HCl
I
O
OH
Rsub
1. NaH, pyridine
2. CuBr•SMe2, reflux
O
Rsub
O
XXXIV

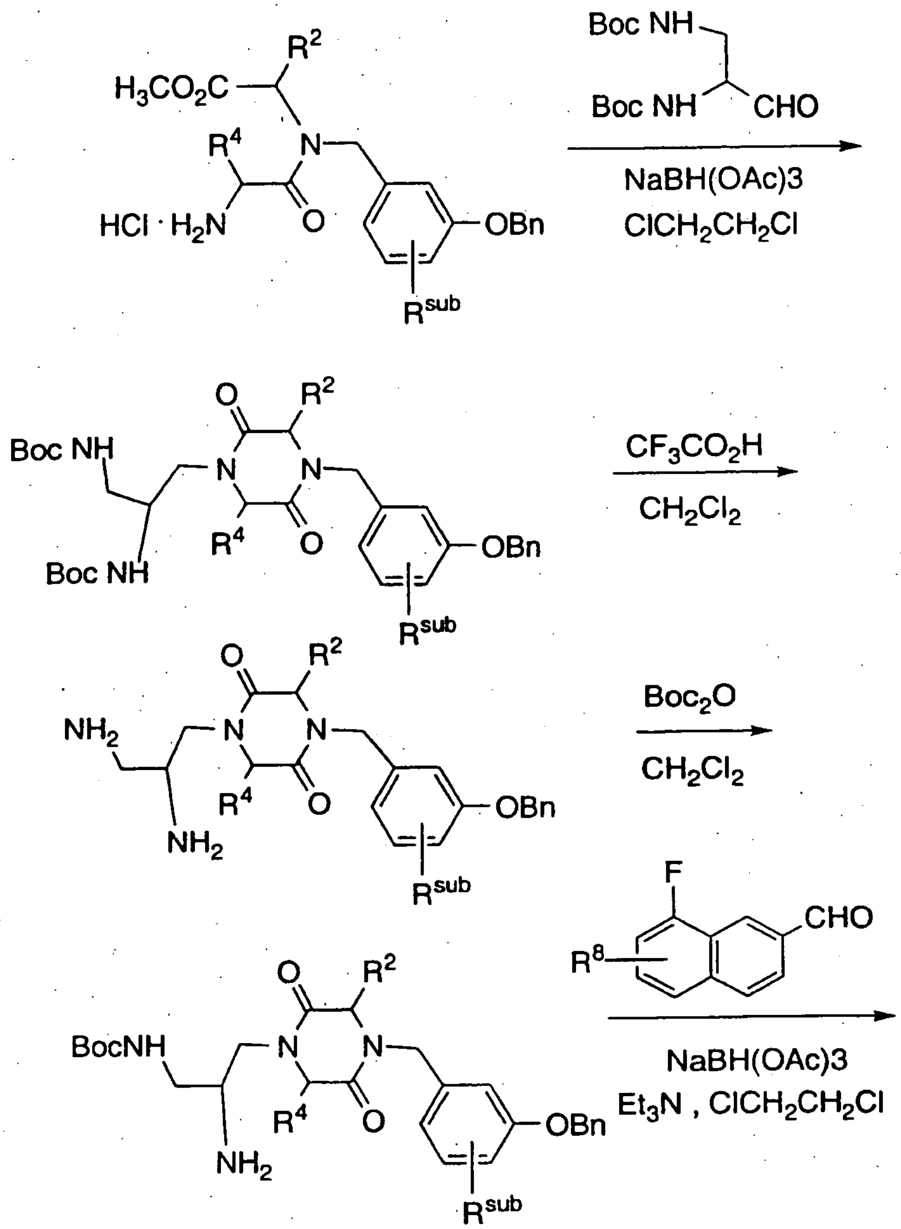
SCHEME 80


H2N
OBn
R2
Rsub
H3CO2C
Br
K2CO3
H3CO2C
N
H
OBn
Rsub
Boc-HN
O
Cl
R4
Et3N
H3CO2C
R2
R4
N
OBn
Boc-HN
O
Rsub
HCl
EtOAc
H3CO2C
R2
R4
N
OBn
HCl · H2N
O
Rsub

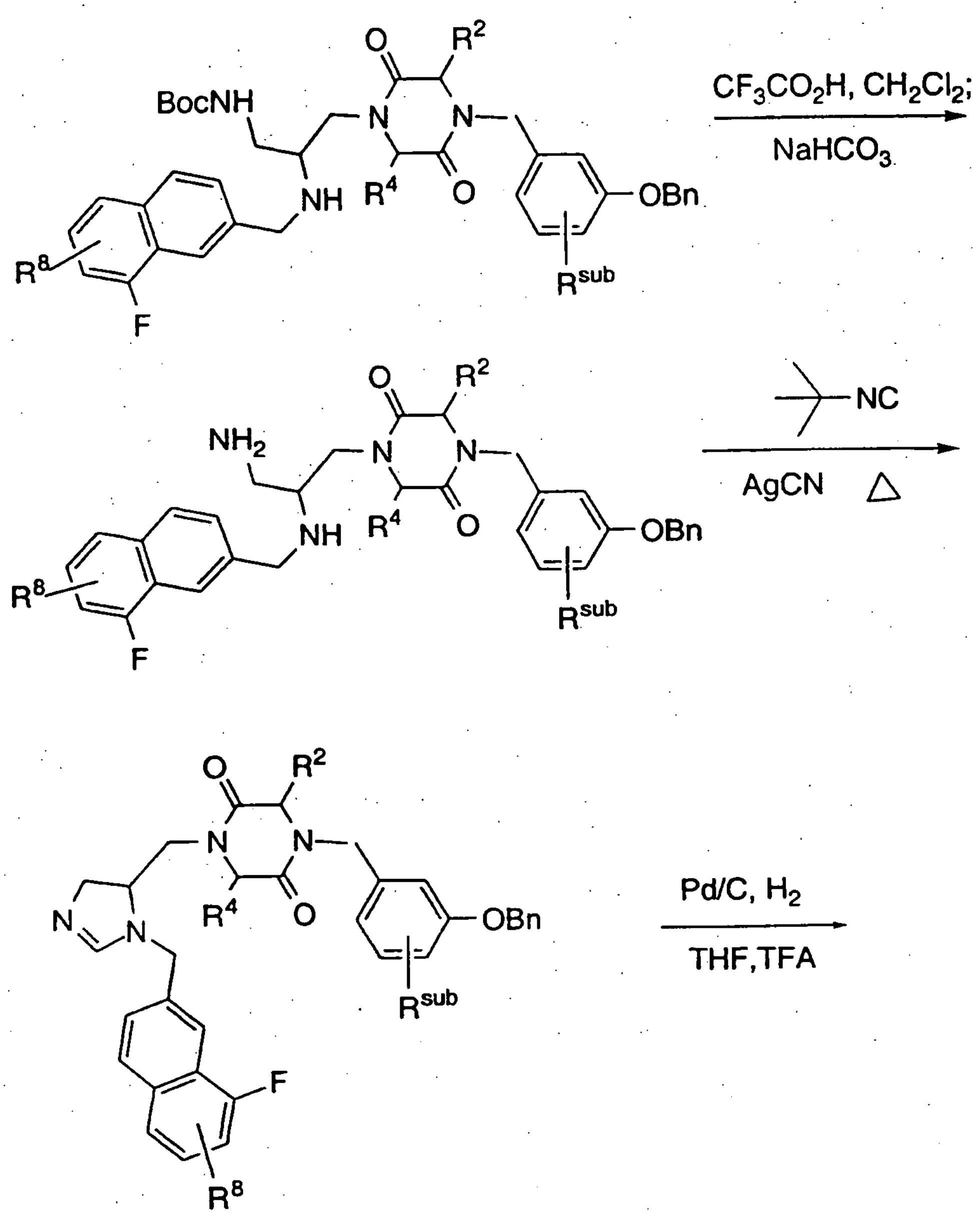
SCHEME 80 (continued)



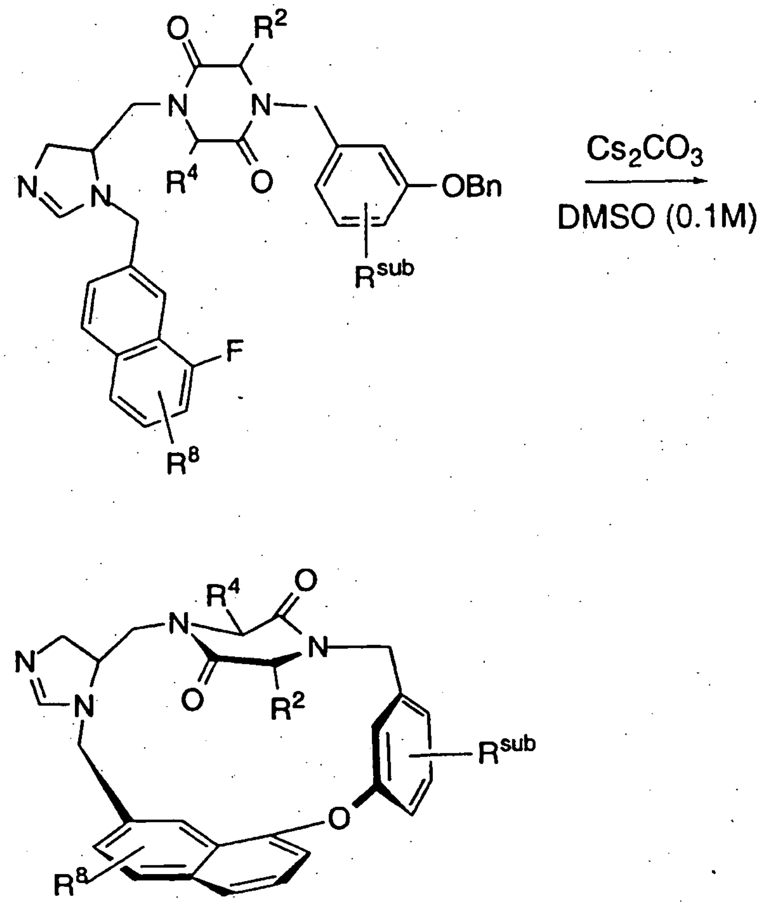
SCHEME 81



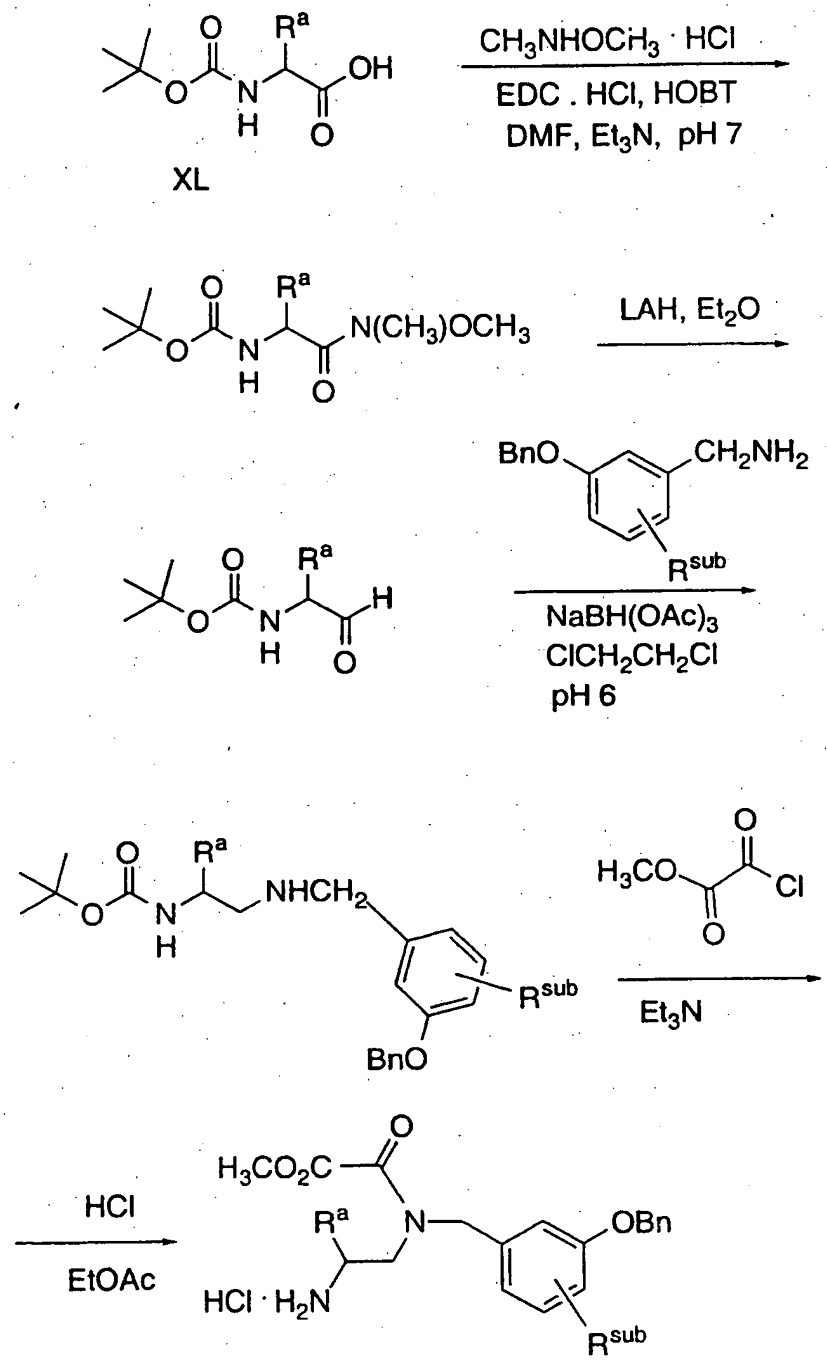
SCHEME 81 (continued)



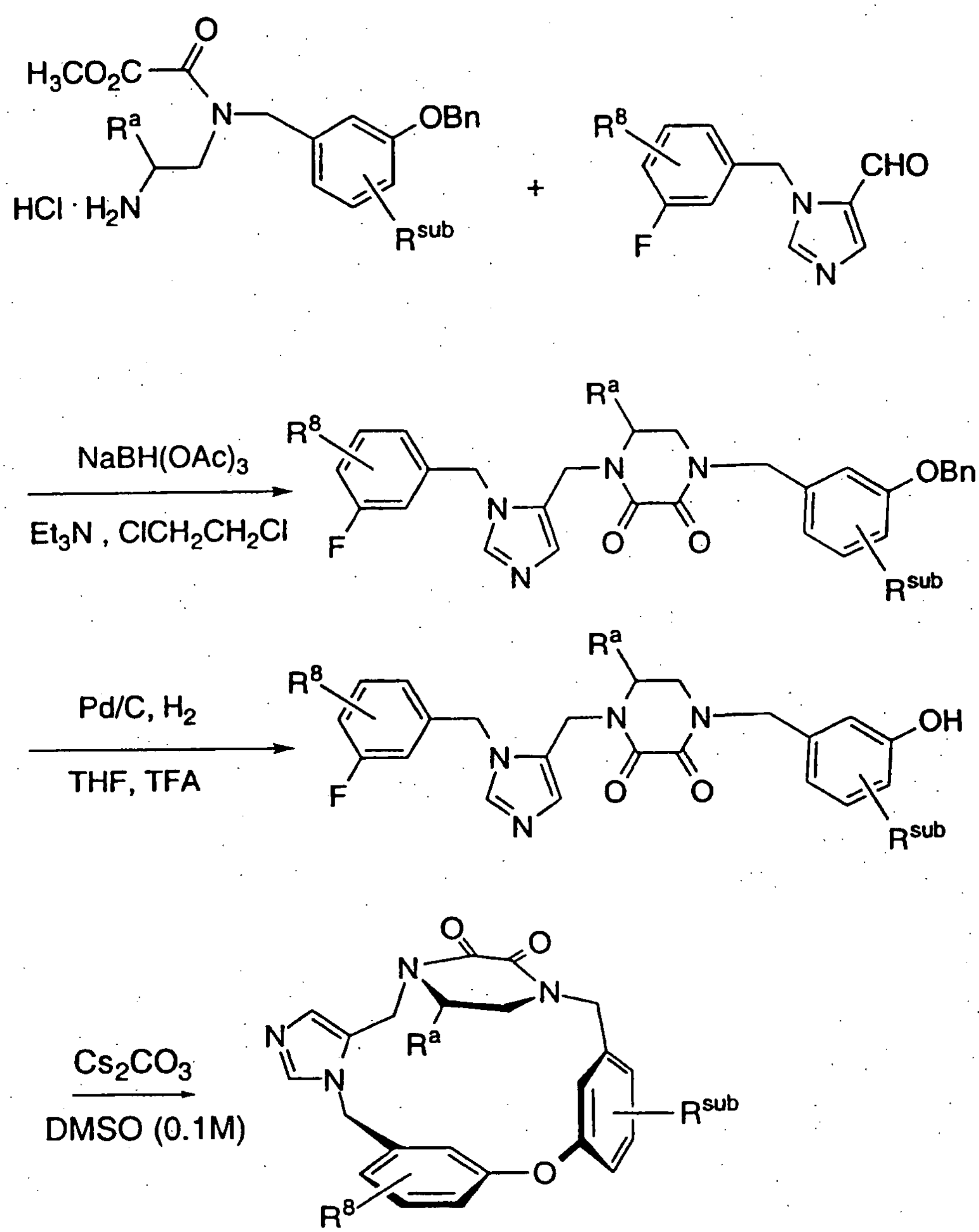
SCHEME 81 (continued)



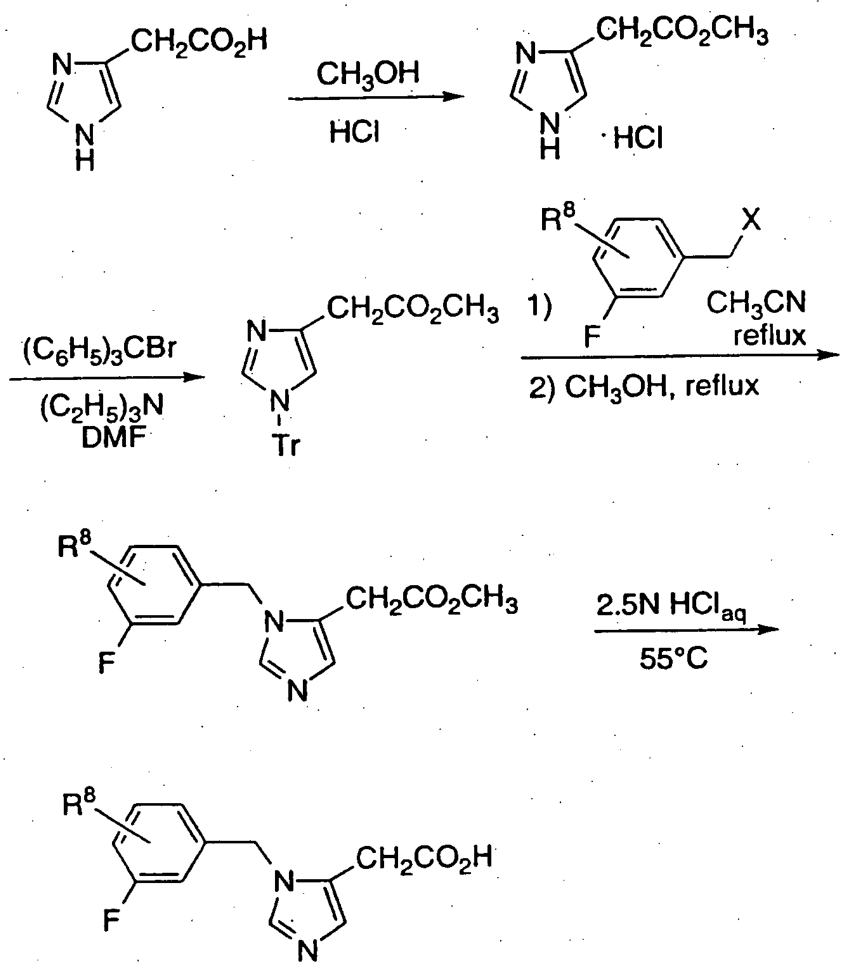
SCHEME 82


XL
$CH_3NHOCH_3 \cdot HCl$
EDC . HCl, HOBT
DMF, Et_3N, pH 7
$N(CH_3)OCH_3$
LAH, Et_2O
BnO
CH_2NH_2
R^{sub}
$NaBH(OAc)_3$
$ClCH_2CH_2Cl$
pH 6
$NHCH_2$
H_3CO
Cl
Et_3N
HCl
EtOAc
H_3CO_2C
OBn
$HCl \cdot H_2N$

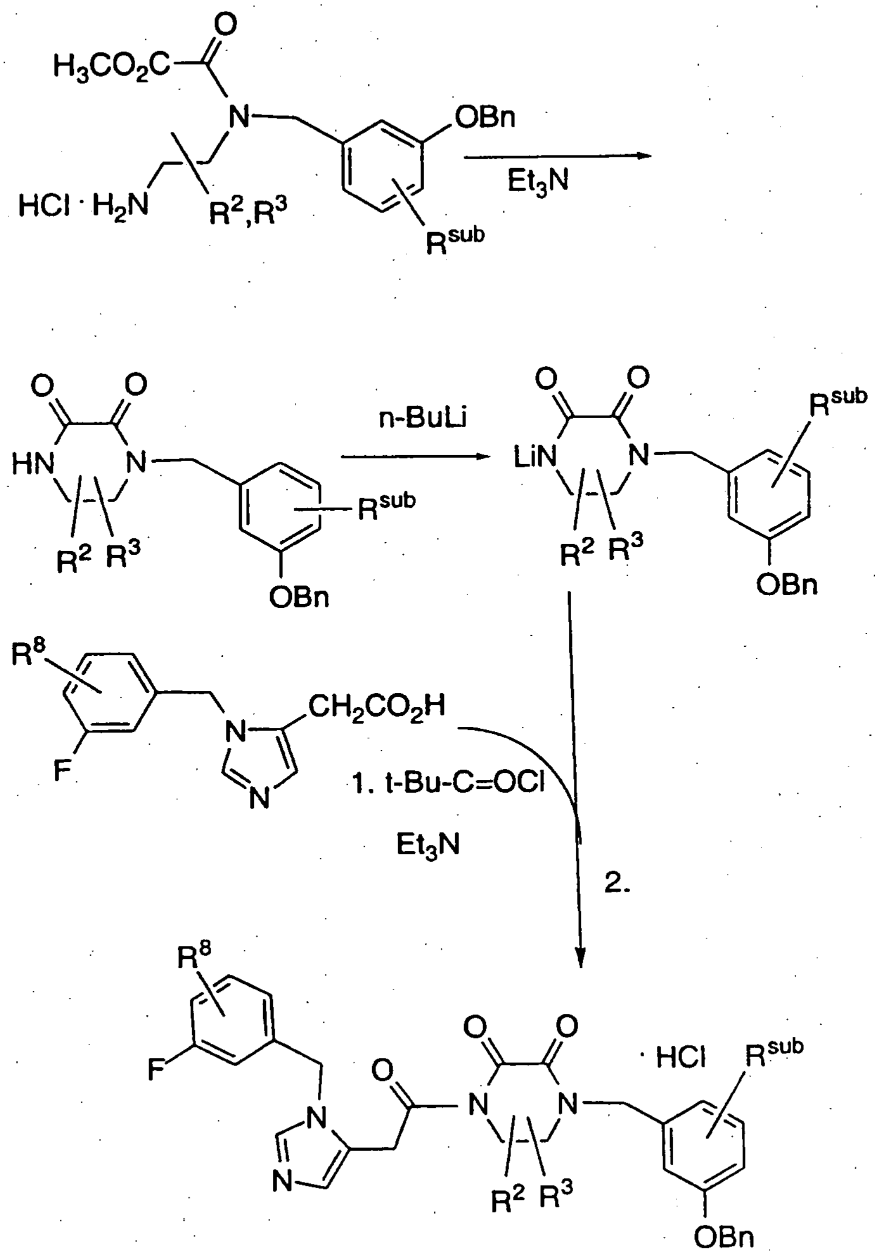
SCHEME 82 (continued)



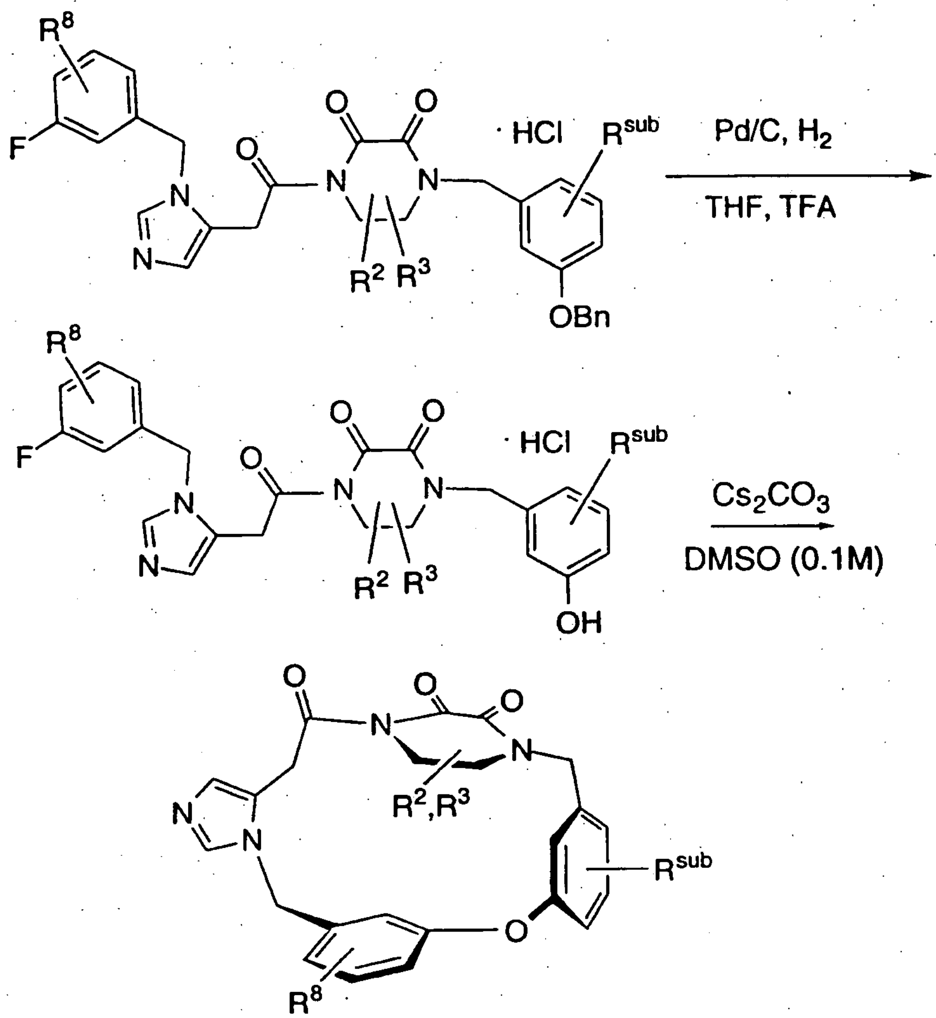
SCHEME 83


CH2CO2H
CH3OH
HCl
CH2CO2CH3
· HCl
R8
X
(C6H5)3CBr
(C2H5)3N
DMF
Tr
1)
CH3CN
reflux
F
2) CH3OH, reflux
2.5N HClaq
55°C

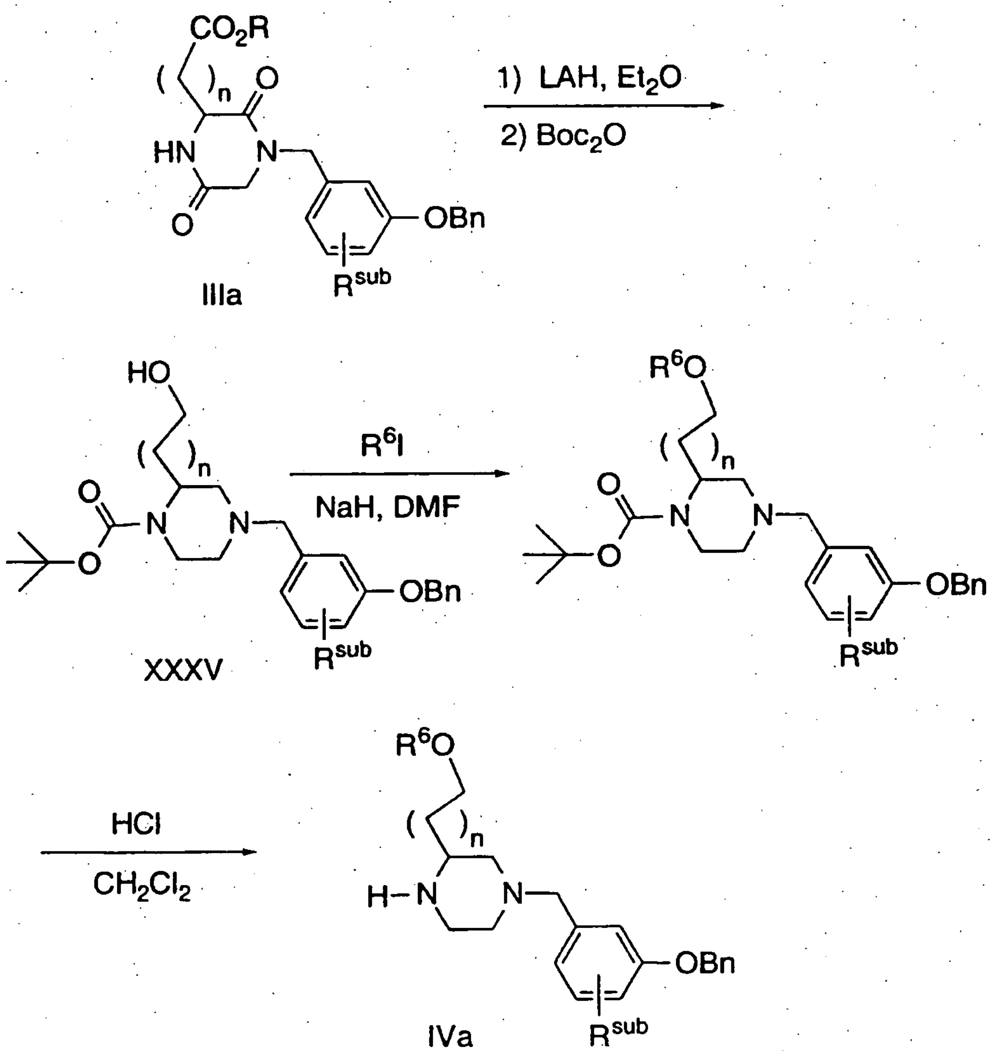
SCHEME 83 (continued)



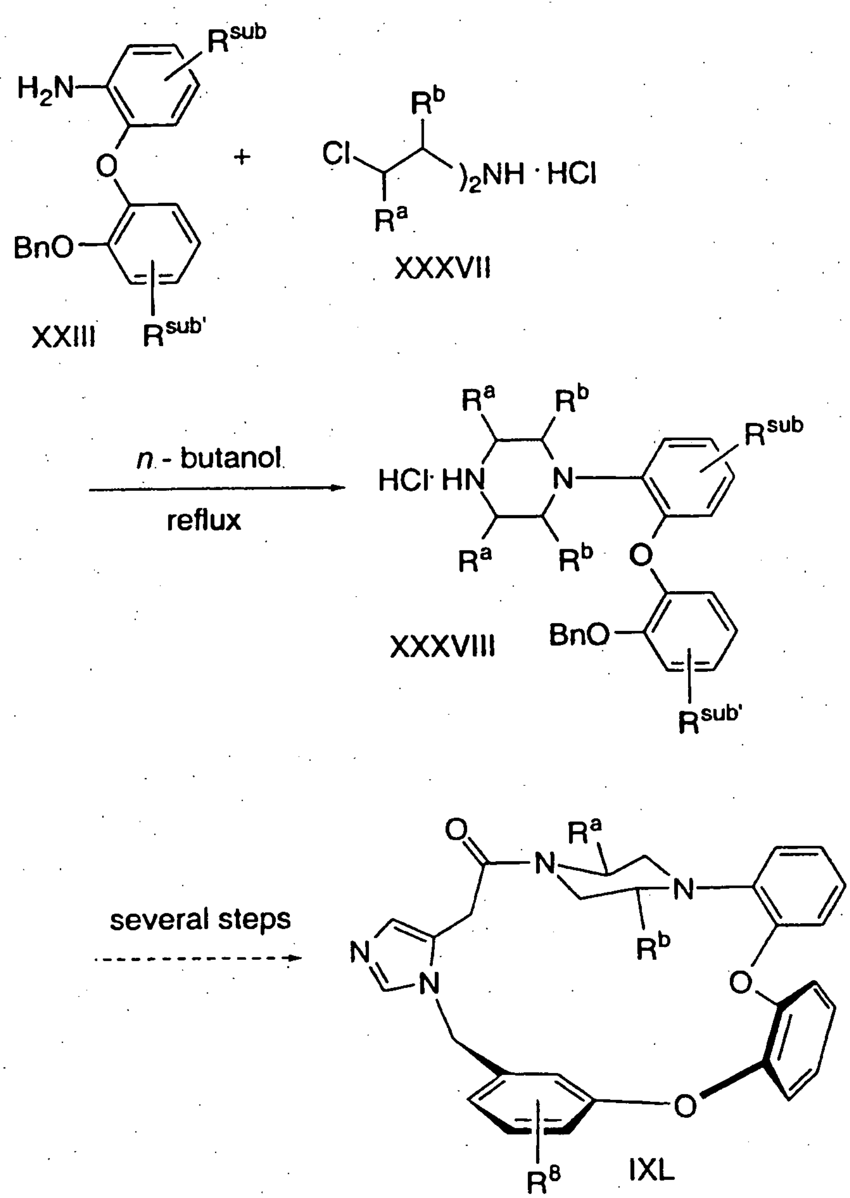
SCHEME 83 (continued)



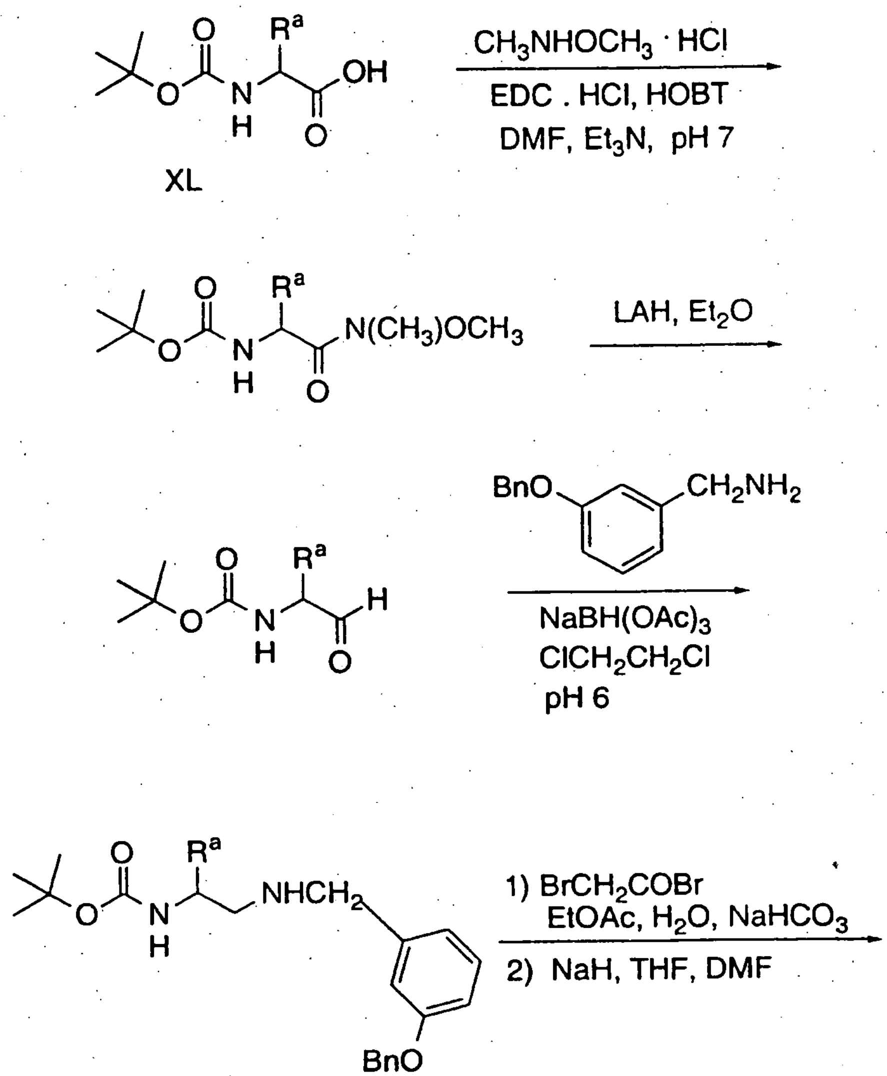
SCHEME 84



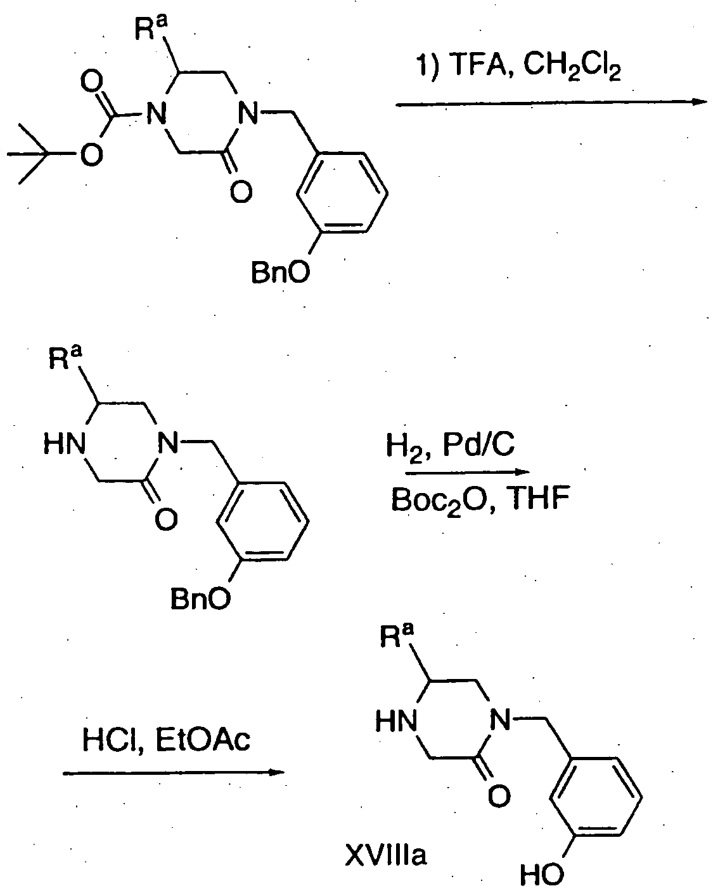
SCHEME 85


H2N
Rsub
O
BnO
Rsub'
XXIII
+
Rb
Cl
)2NH · HCl
Ra
XXXVII
n - butanol
reflux
Ra
Rb
HCl· HN
N
Rsub
Ra
Rb
O
XXXVIII
BnO
Rsub'
several steps
O
Ra
N
N
N
N
Rb
O
O
R8
IXL

SCHEME 86

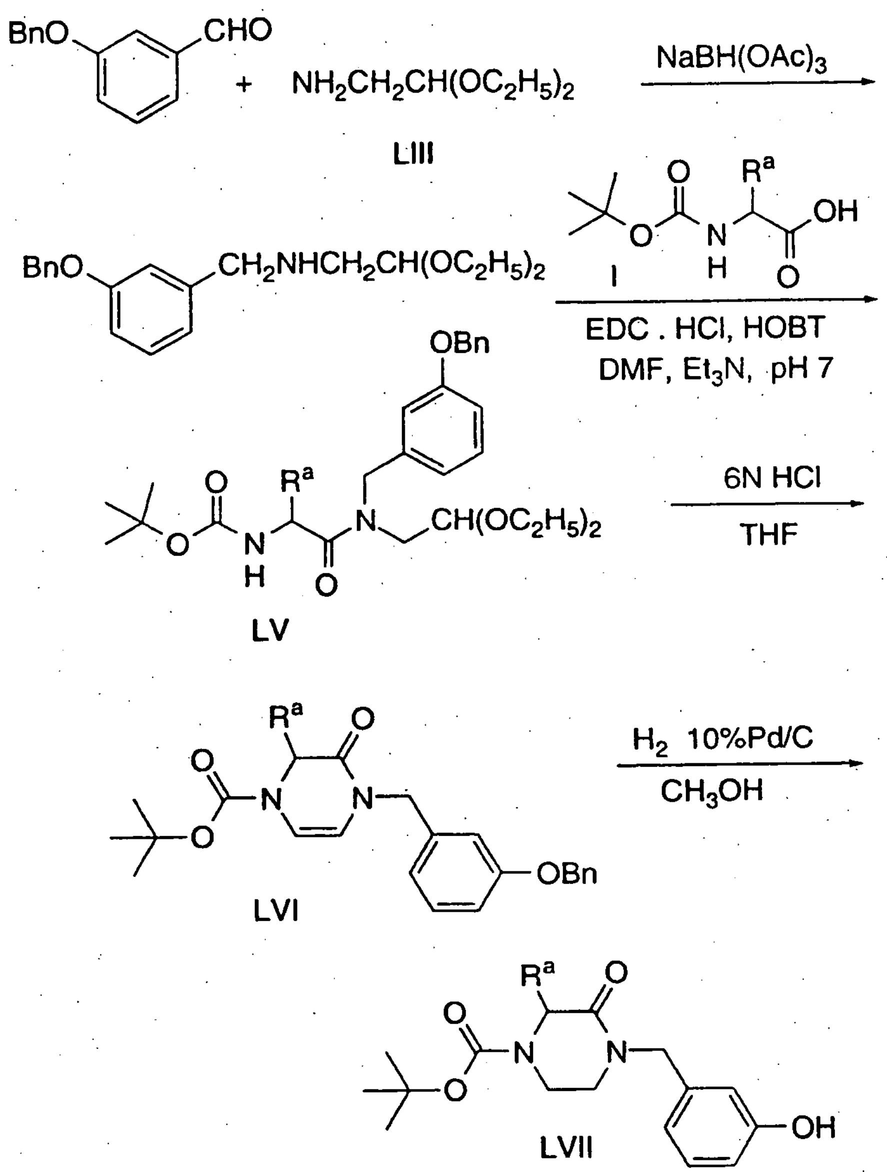

R^a
OH
N
H
O
XL
CH3NHOCH3 · HCl
EDC . HCl, HOBT
DMF, Et3N, pH 7
N(CH3)OCH3
LAH, Et2O
H
BnO
CH2NH2
NaBH(OAc)3
ClCH2CH2Cl
pH 6
NHCH2
1) BrCH2COBr
EtOAc, H2O, NaHCO3
2) NaH, THF, DMF

SCHEME 86 (CONT'D)

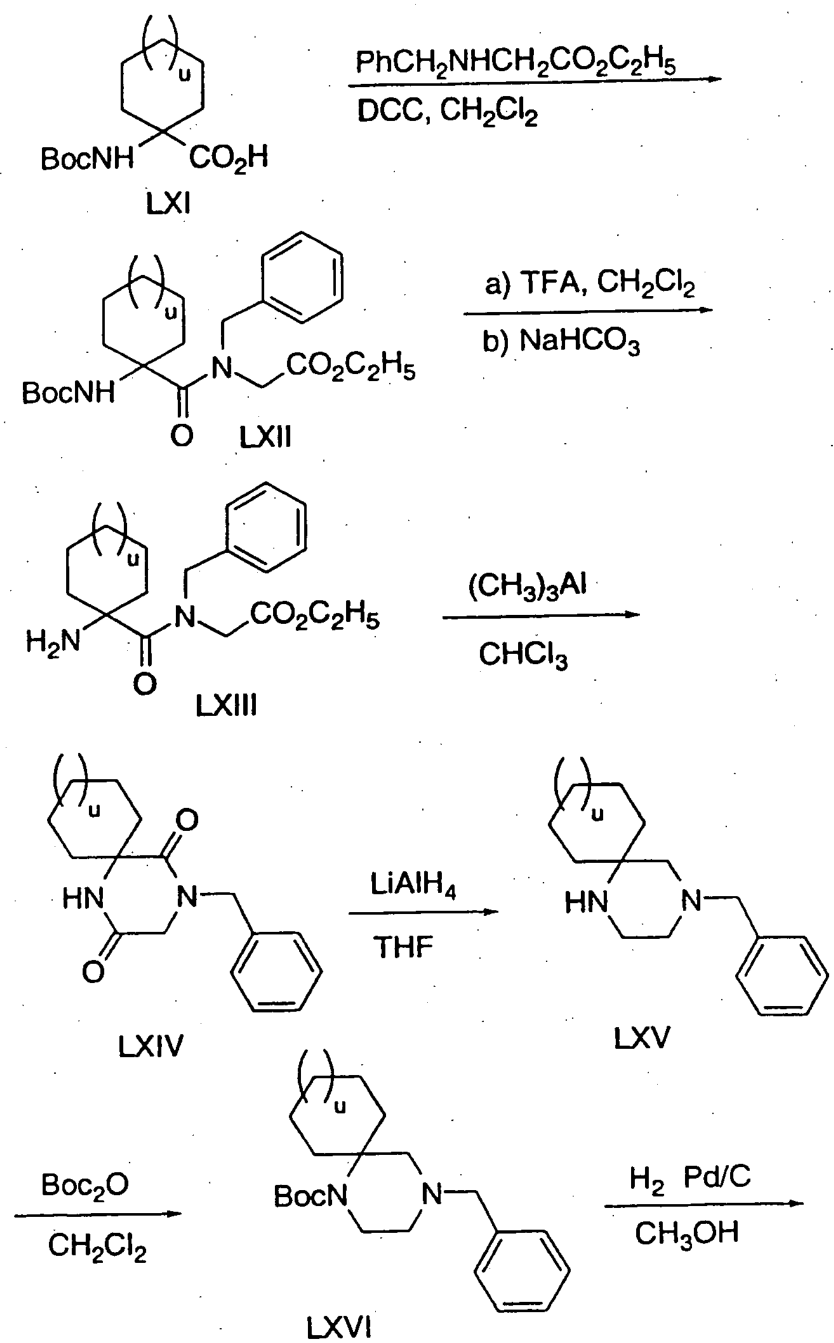


XVIIIa

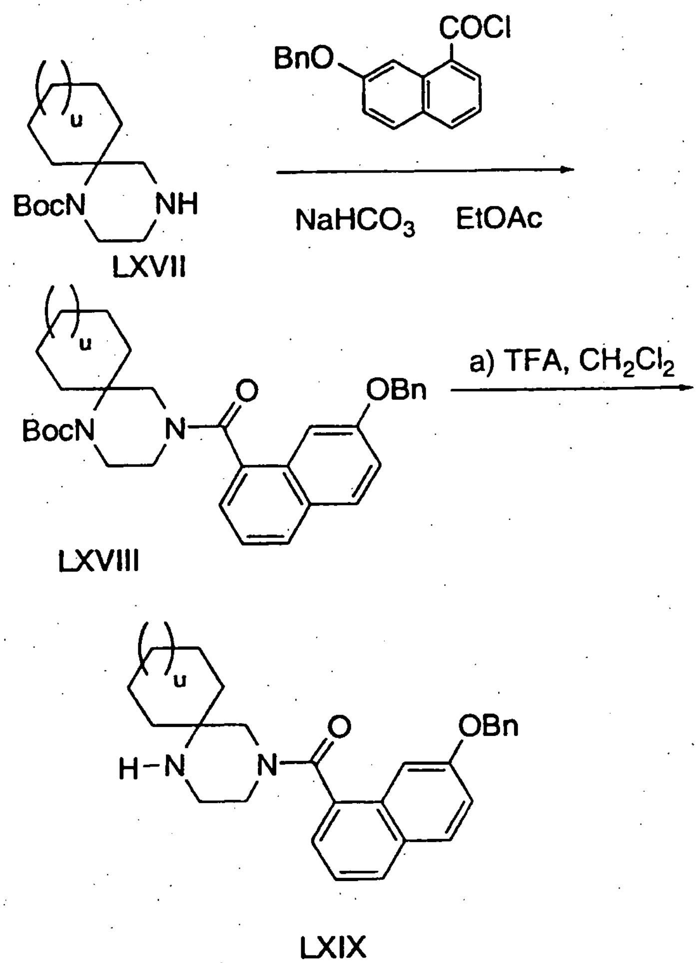
SCHEME 87



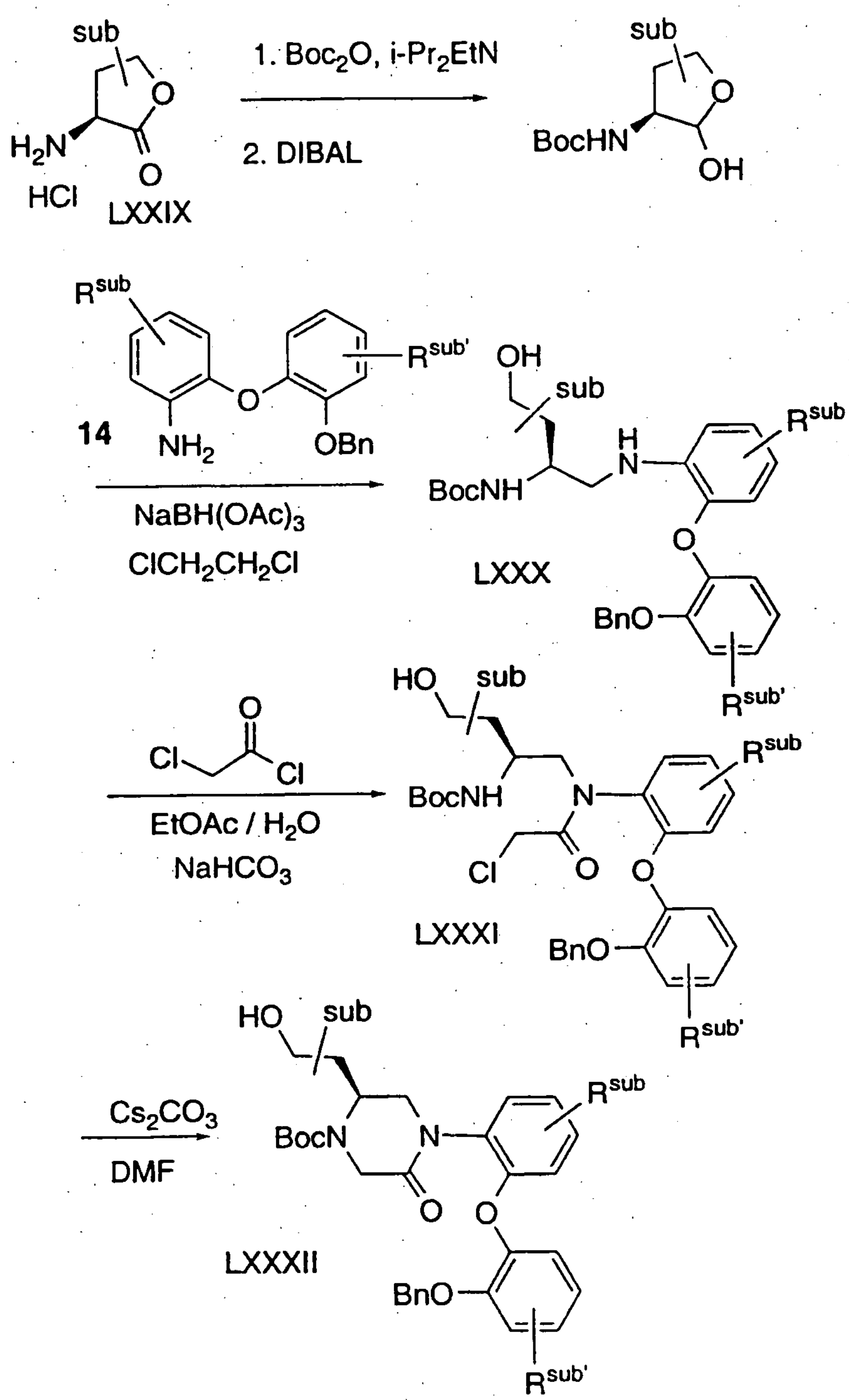
SCHEME 88



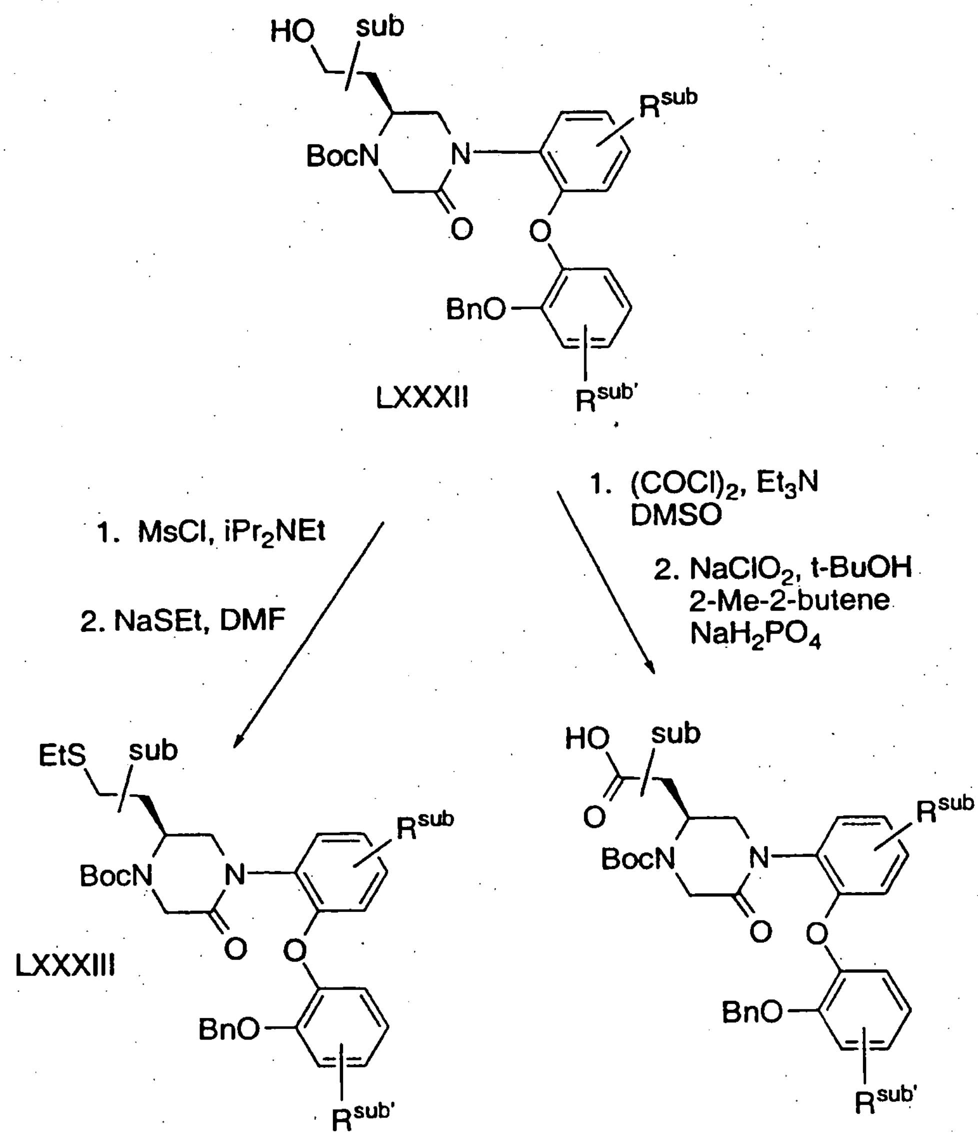
SCHEME 88 (continued)



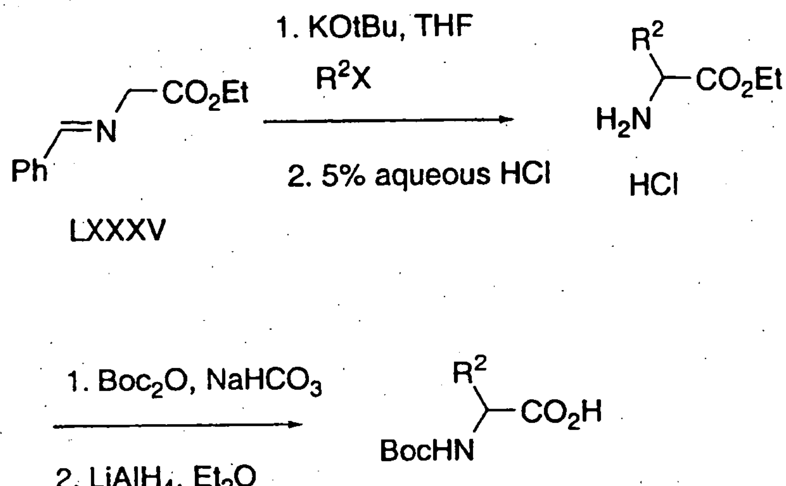
SCHEME 89


sub
H_2N
HCl
LXXIX
1. Boc_2O, i-Pr_2EtN
2. DIBAL
BocHN
OH
R^{sub}
$R^{sub'}$
14
NH_2
OBn
$NaBH(OAc)_3$
$ClCH_2CH_2Cl$
OH
BocNH
LXXX
BnO
Cl
EtOAc / H_2O
$NaHCO_3$
HO
LXXXI
Cs_2CO_3
DMF
BocN
LXXXII

SCHEME 89 (continued)



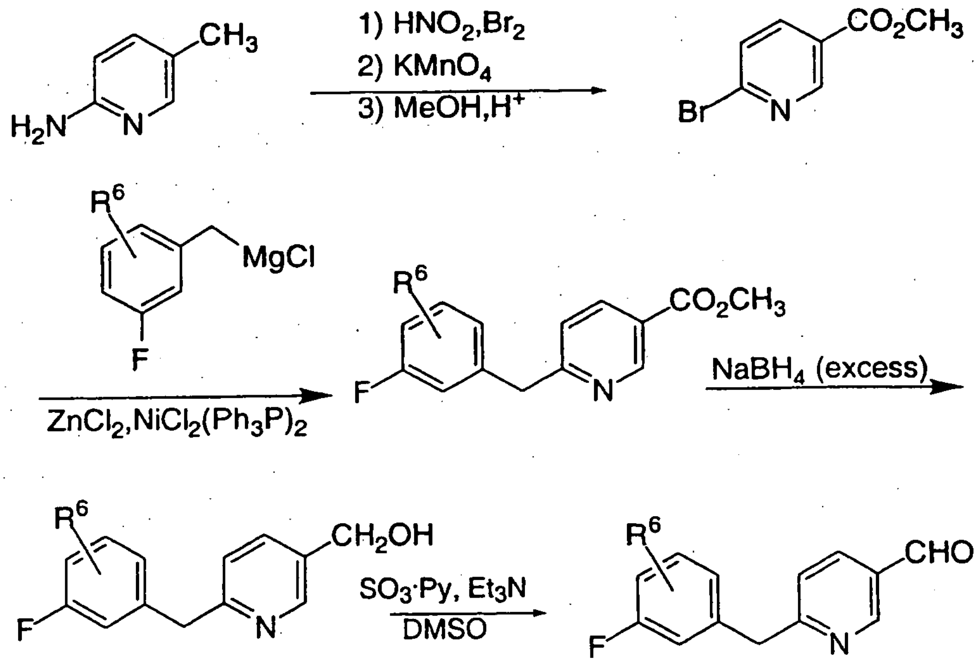
SCHEME 90



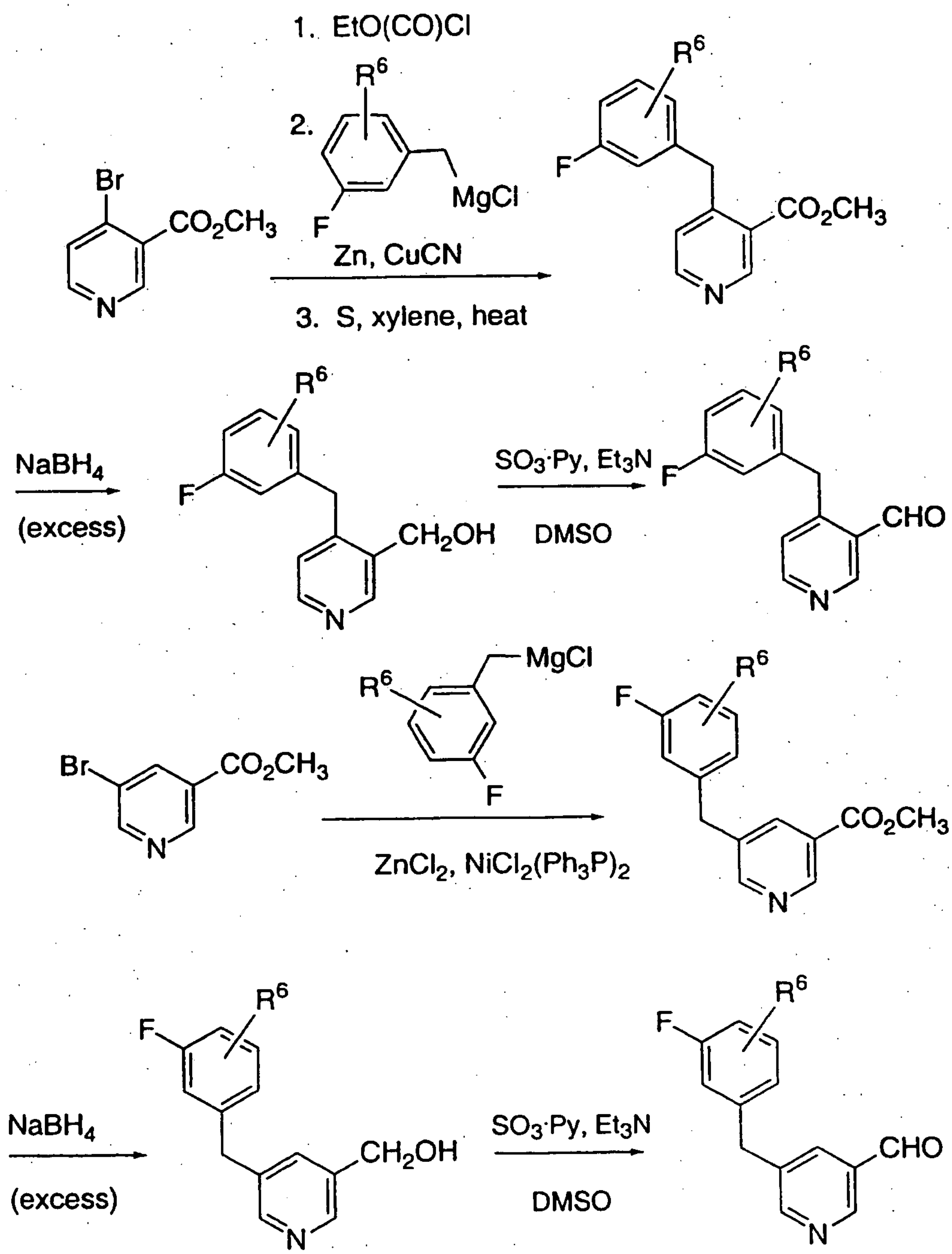
LXXXV

LXXXVI

SCHEME 91

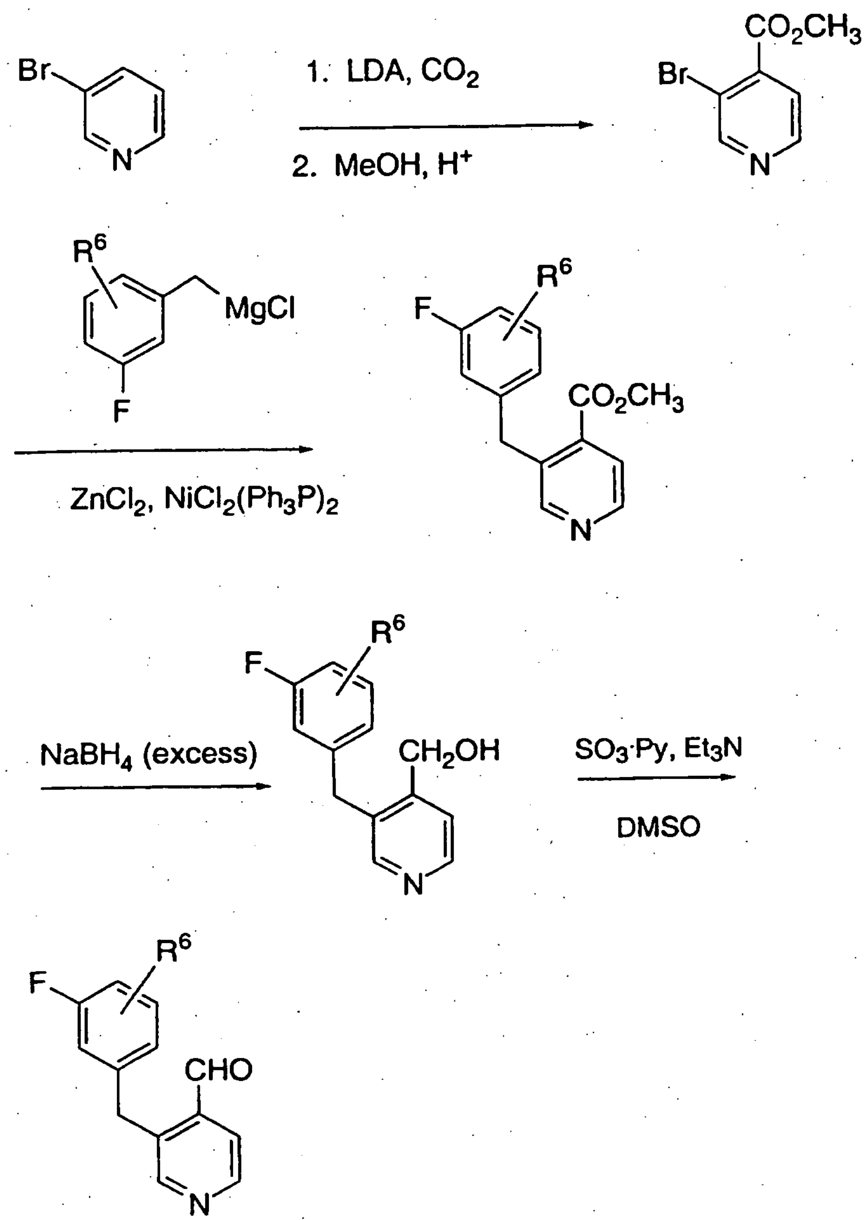


SCHEME 92



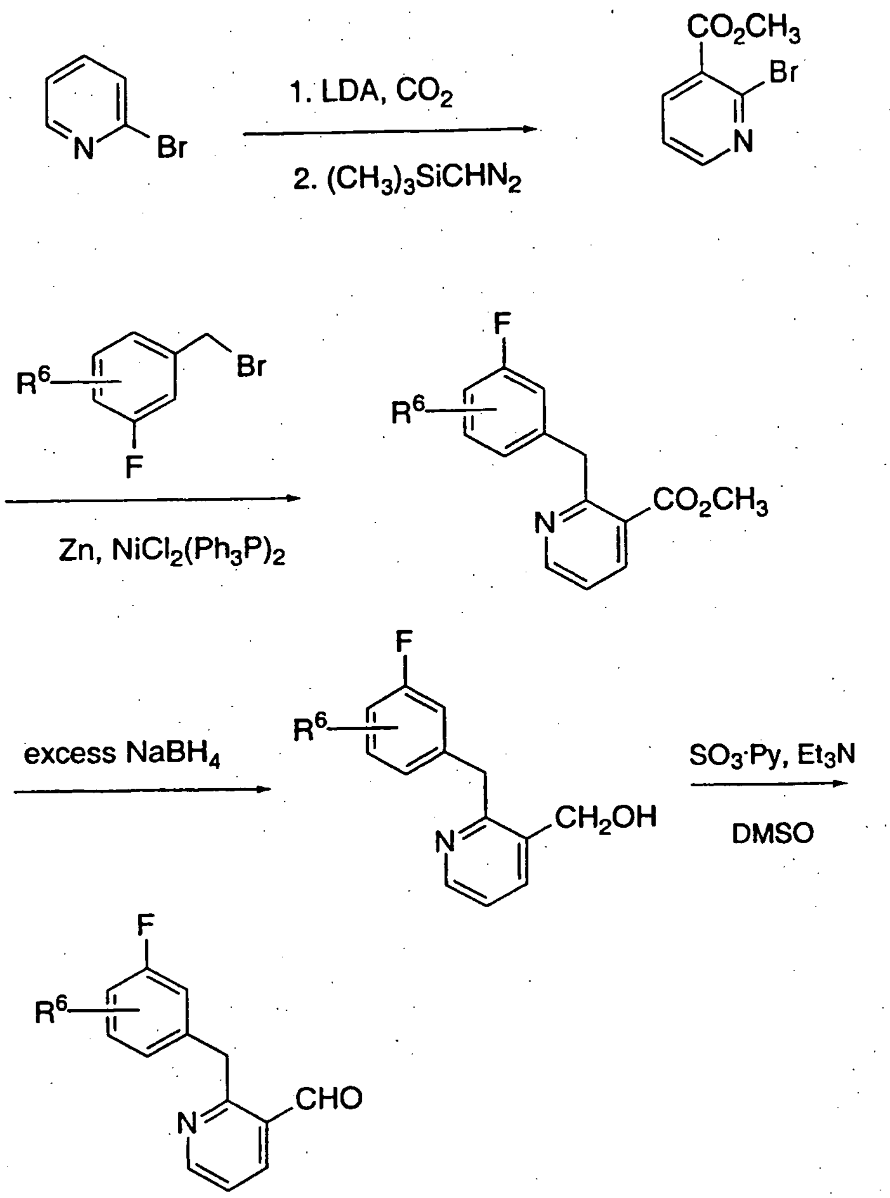
1. EtO(CO)Cl
2.
R6
MgCl
F
Zn, CuCN
3. S, xylene, heat
Br
CO2CH3
N
NaBH4
(excess)
CH2OH
SO3·Py, Et3N
DMSO
CHO
ZnCl2, NiCl2(Ph3P)2

SCHEME 93



Br
1. LDA, CO2
2. MeOH, H+
CO2CH3
Br
N
R6
MgCl
F
ZnCl2, NiCl2(Ph3P)2
F
R6
CO2CH3
N
NaBH4 (excess)
F
R6
CH2OH
N
SO3·Py, Et3N
DMSO
F
R6
CHO
N

SCHEME 94



The compounds of the formula (V) are prepared by employing reactions as shown in the Schemes 95-100, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exempli-

fied in the experimental procedures. Substituents R, R^a, R^b and R^{sub}, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5, and substituents on Z^1 and Z^2; however their point of attachment to the ring is illustrative only and is not meant to be limiting. The compounds referred to in the Synopsis of Schemes 95-100 by Roman numerals are numbered starting sequentially with I and ending with XVIII.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

<u>Synopsis of Schemes 95-100:</u>

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. For example, syntheses of instant compounds wherein the linker "X" is an sulfonamido linkage is illustrated in Scheme 95. Thus, a suitably substituted benzylimidazolyl containing amine I is prepared as illustrated. A suitably substituted benzyl alcohol II is converted to the corresponding benzylsulfinylchloride III. Reaction of intermediate III with the primary amine I provides the sulfinamido intermediate IV. That intermediate can be oxidized to the sulfonamide, the alcohol moiety can then be deprotected and previously described intramolecular cyclization provides compound V of the instant invention.

Instant compounds wherein the variable "V" is other than a phenyl moiety can be prepared as illustrated in Scheme 96. Thus, a suitably substituted fluoronaphthylmethyl bromide VII may be reacted with an imidazolyl alkylacetate to provide intermediate VIII. The alcohol moiety of intermediate VIII can be deprotected and then reacted with a suitably substituted phenyl isocyanate to provide the carbamate IX, which may then be optionally N-alkylated, followed by deprotection and intramolecular cyclization to provide compound XI of the instant invention.

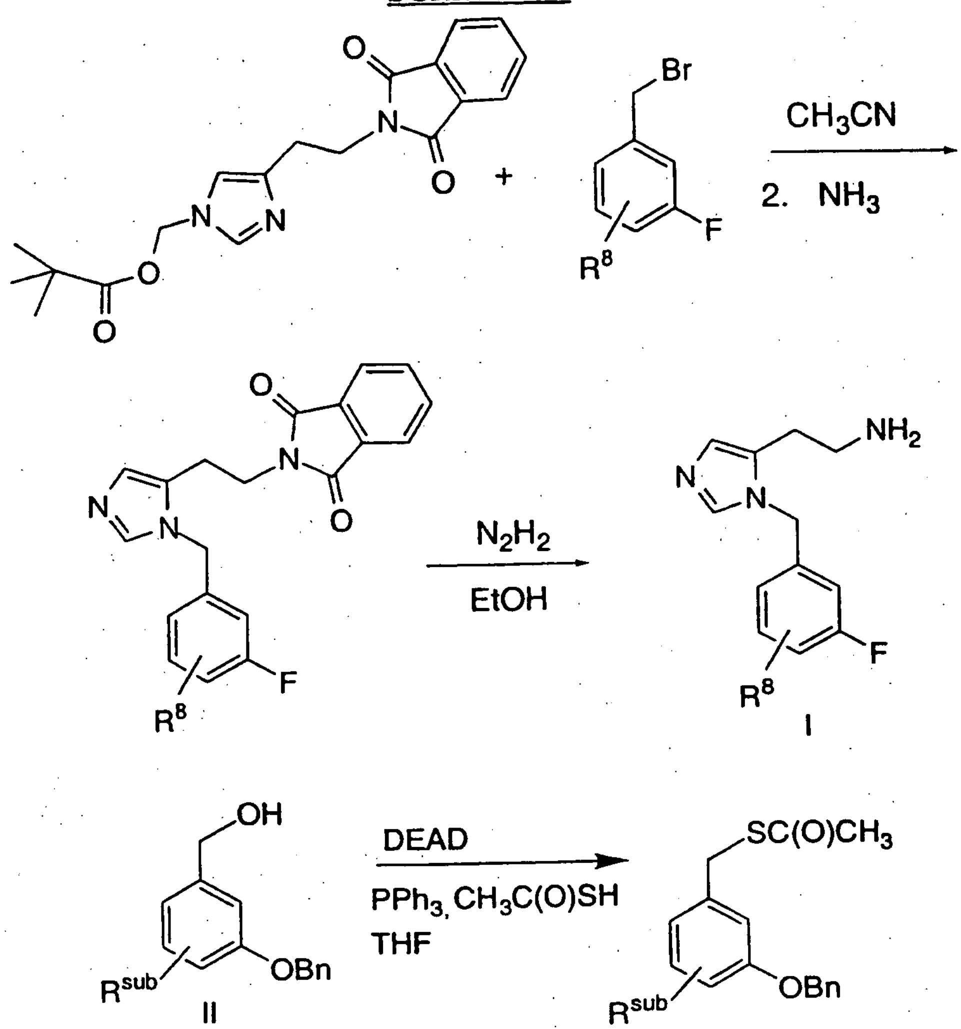
Synthesis of compounds of the instant invention wherein variables "Z^1" and "Z^2" are both phenyl moieties and the linker "X"

is a amido moiety is illustrated in Scheme 97. Scheme 98 illustrates preparation of the corresponding instant compound wherein linker "X" is a urea moiety by reacting the isocyanate derived from intermediate I and the phenoxyanaline XIII described in Scheme 97. Synthesis of compounds of the instant invention wherein variable "Z^1" is a naphthyl moiety and the linker "X" is a amido moiety is illustrated in Scheme 99.

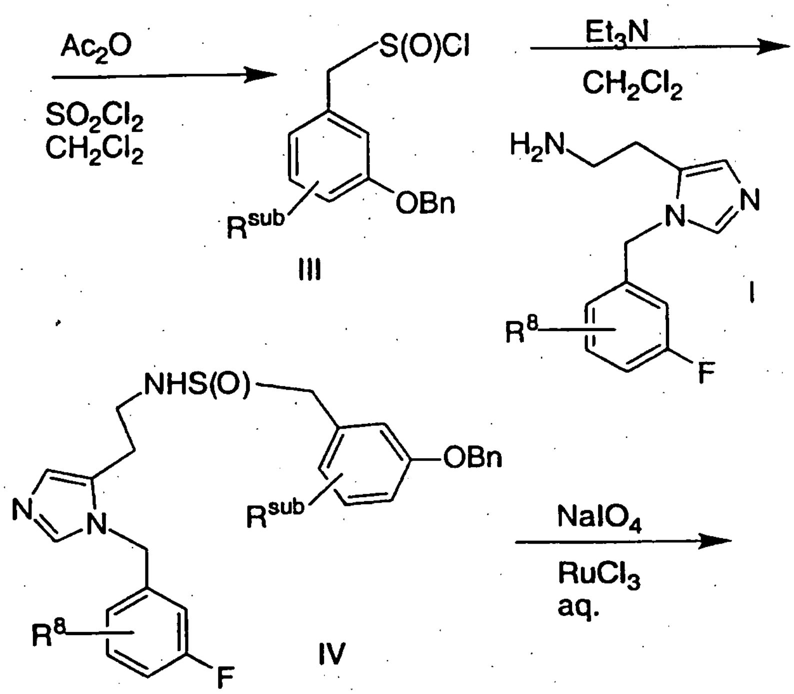
Scheme 100 illustrates the synthetic strategy that is employed when the R^8 substitutent is not an electronic withdrawing moiety either ortho or para to the fluorine atom. In the absence of the electronic withdrawing moiety, the intramolecular cyclization can be accomplished via an Ullmann reaction. Thus, the aldehyde XIV can be converted to the homologous amine XV. Amine XV is then reacted with the previously described benzyloxybenzoic acid XVI to provide intermediate XVII. Intramolecular cyclization may then be affected under Ullmann reaction conditions to provide the amido macrocycle of the instant invention XVIII.

Syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety is shown in Schemes 91-94 hereinabobove. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

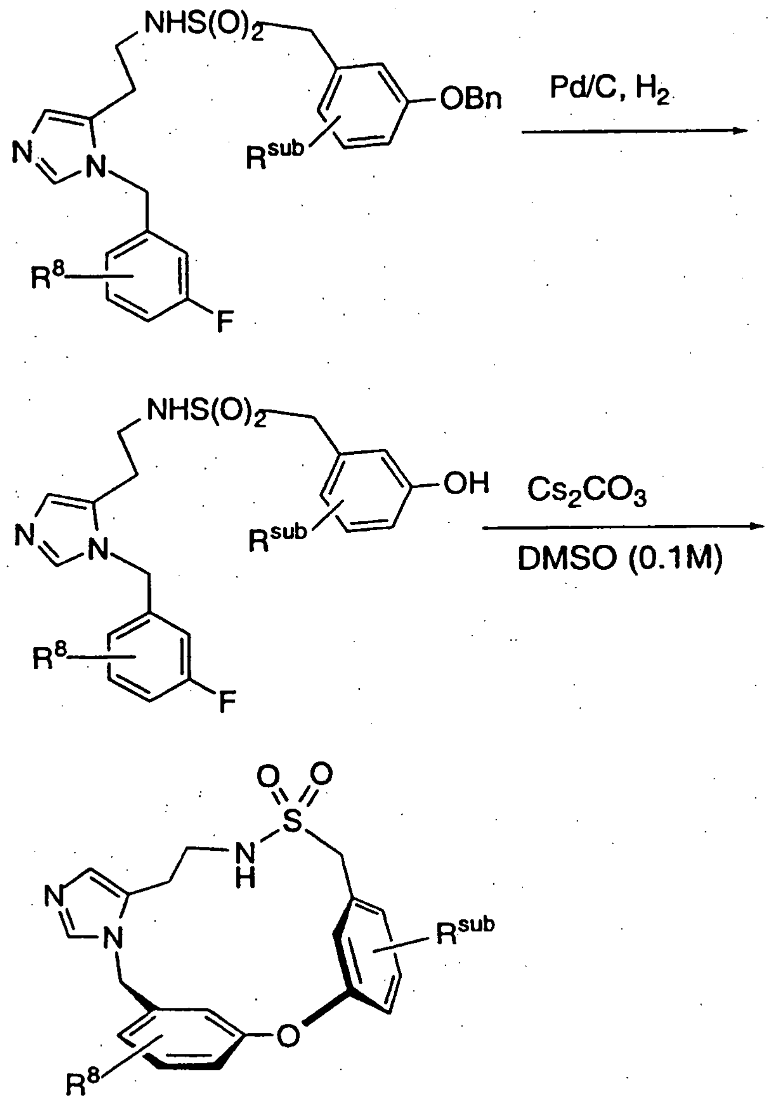
SCHEME 95



SCHEME 95 (continued)

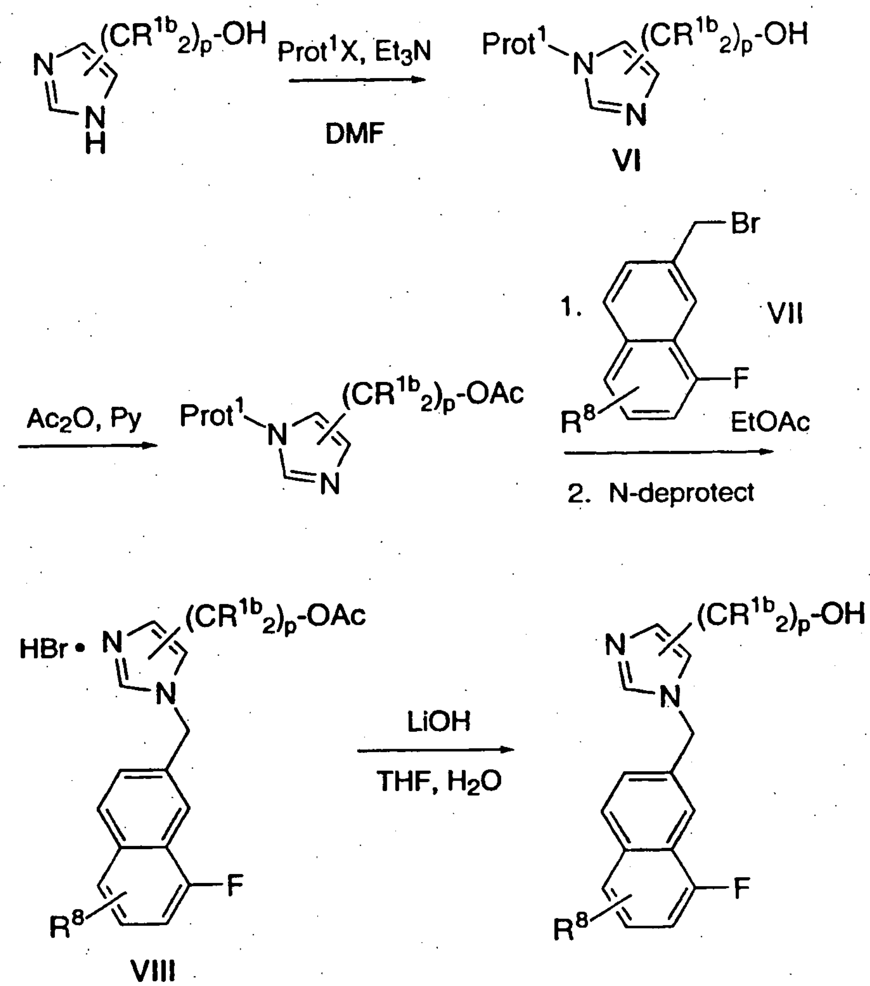


SCHEME 95 (continued)

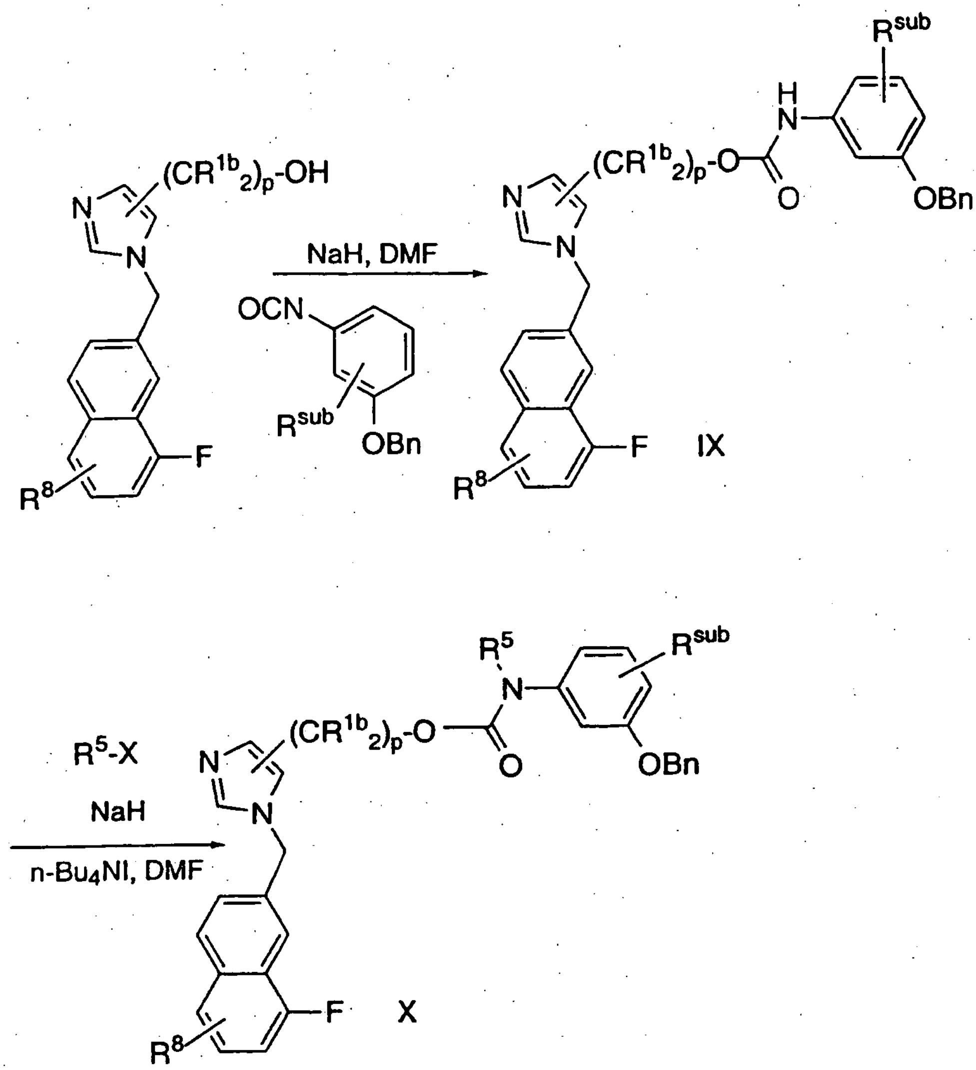


V

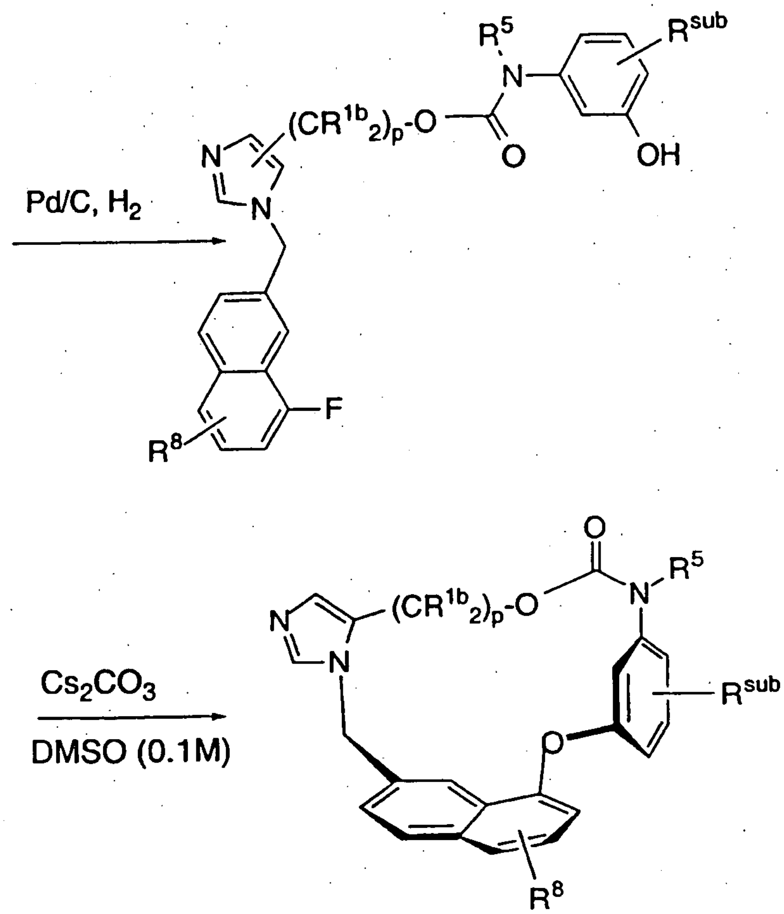
SCHEME 96



SCHEME 96 (continued)

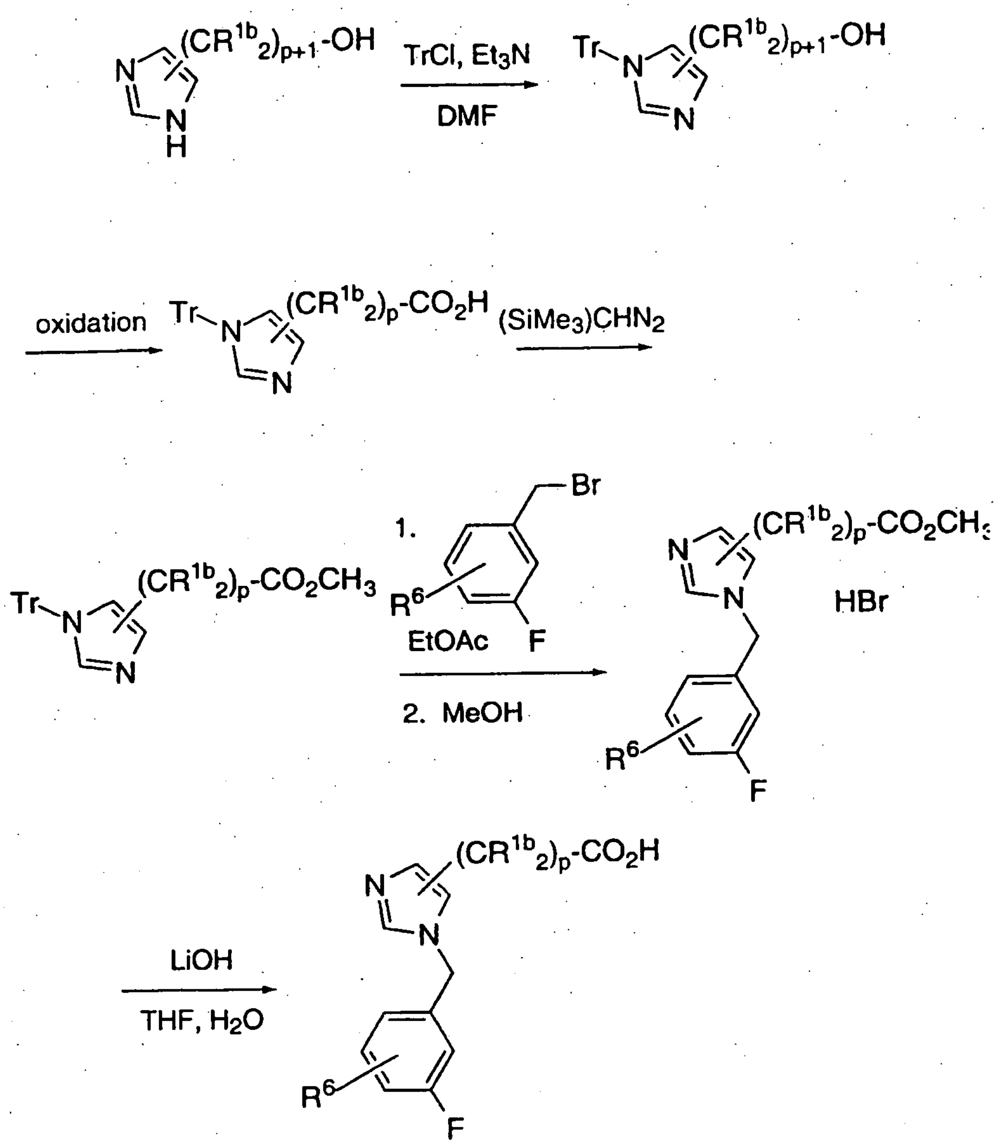


SCHEME 96 (continued)

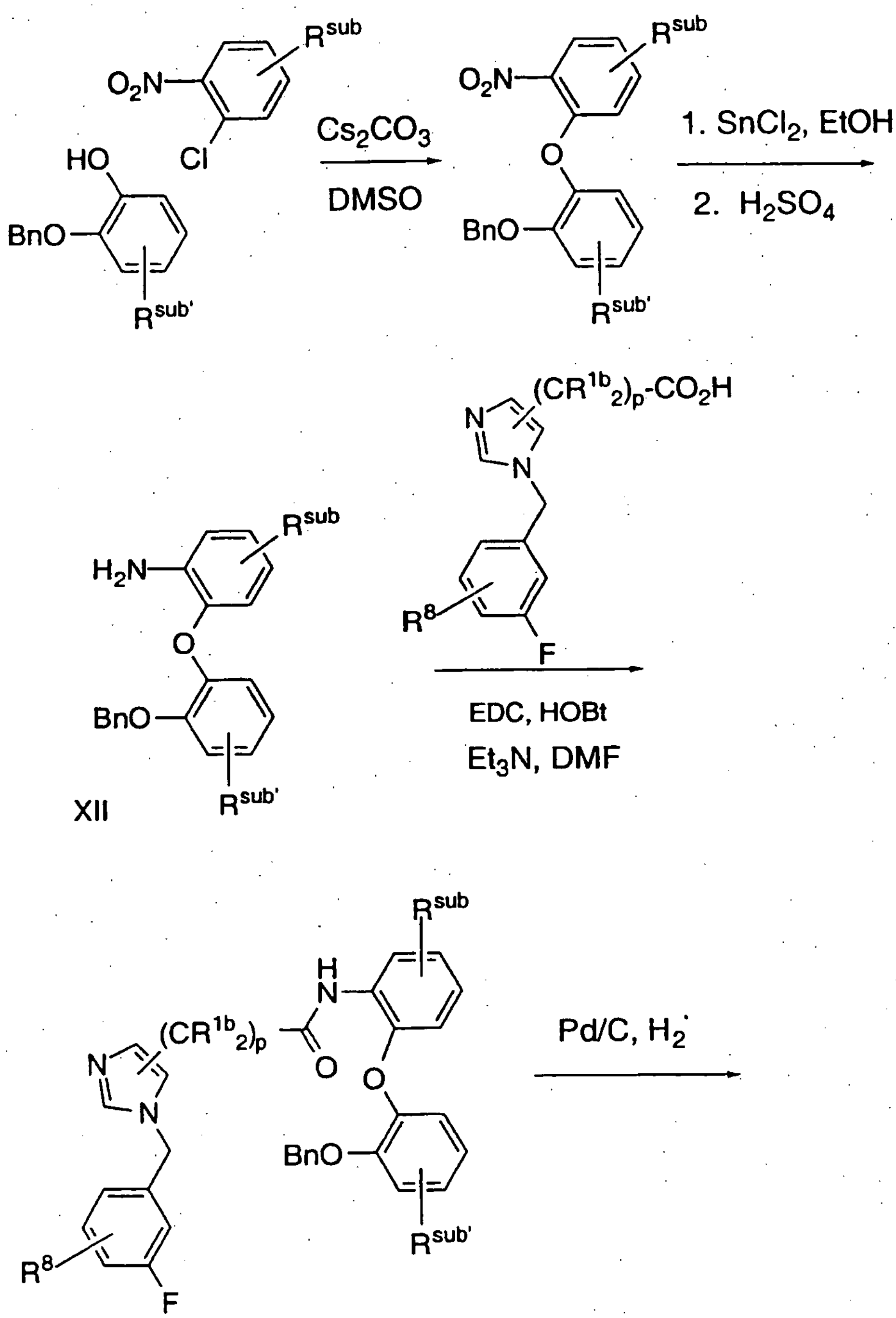


XI

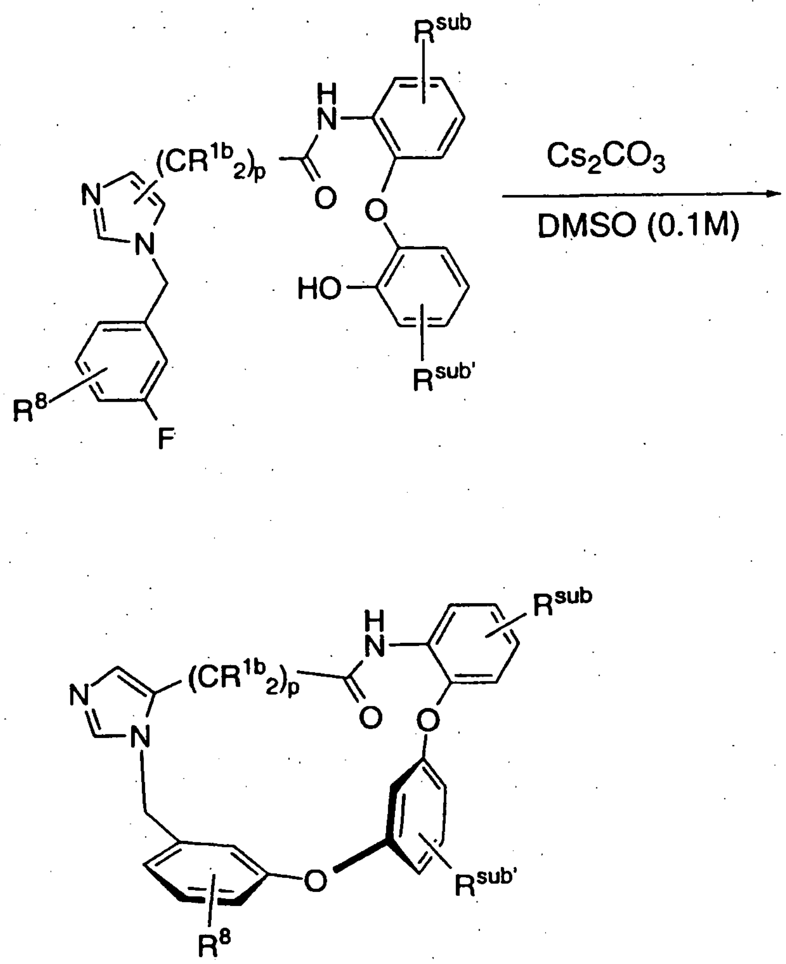
SCHEME 97


(CR1b2)p+1-OH
N
N
H
TrCl, Et3N
DMF
Tr
oxidation
(CR1b2)p-CO2H
(SiMe3)CHN2
(CR1b2)p-CO2CH3
1.
Br
R6
F
EtOAc
2. MeOH
HBr
LiOH
THF, H2O

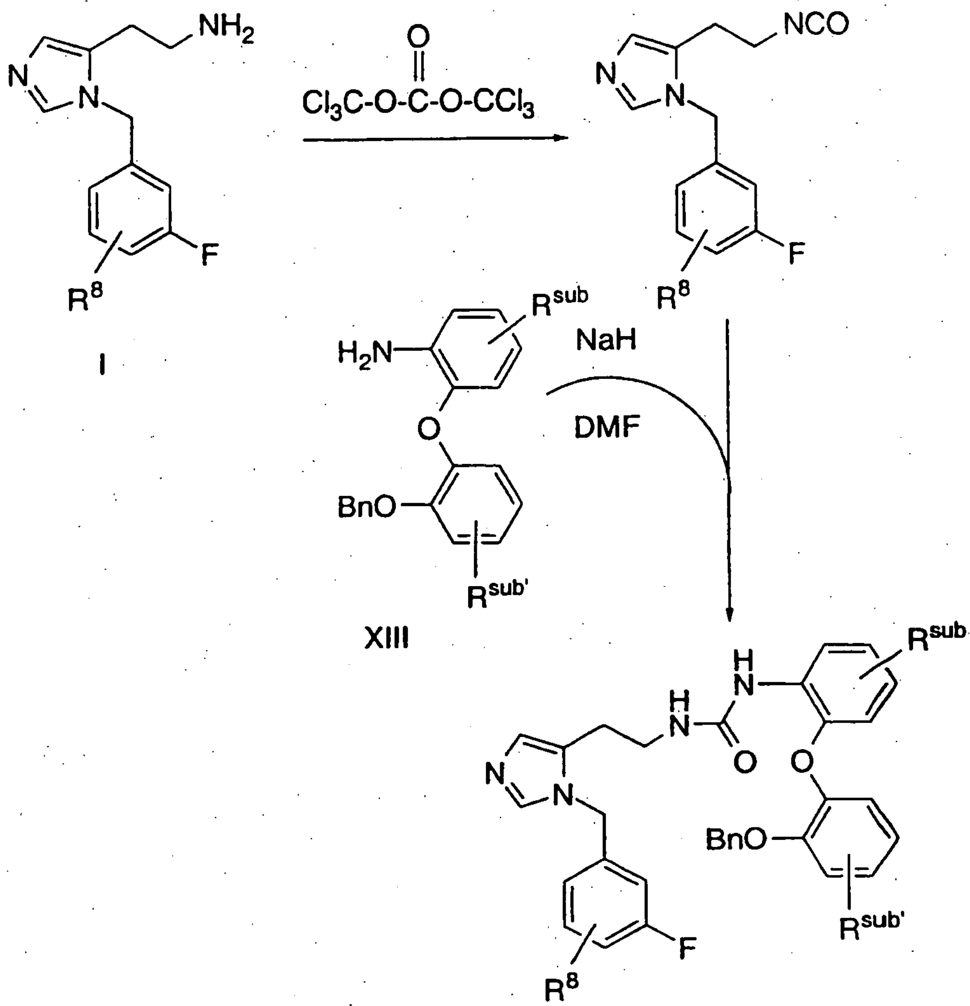
SCHEME 97 (continued)



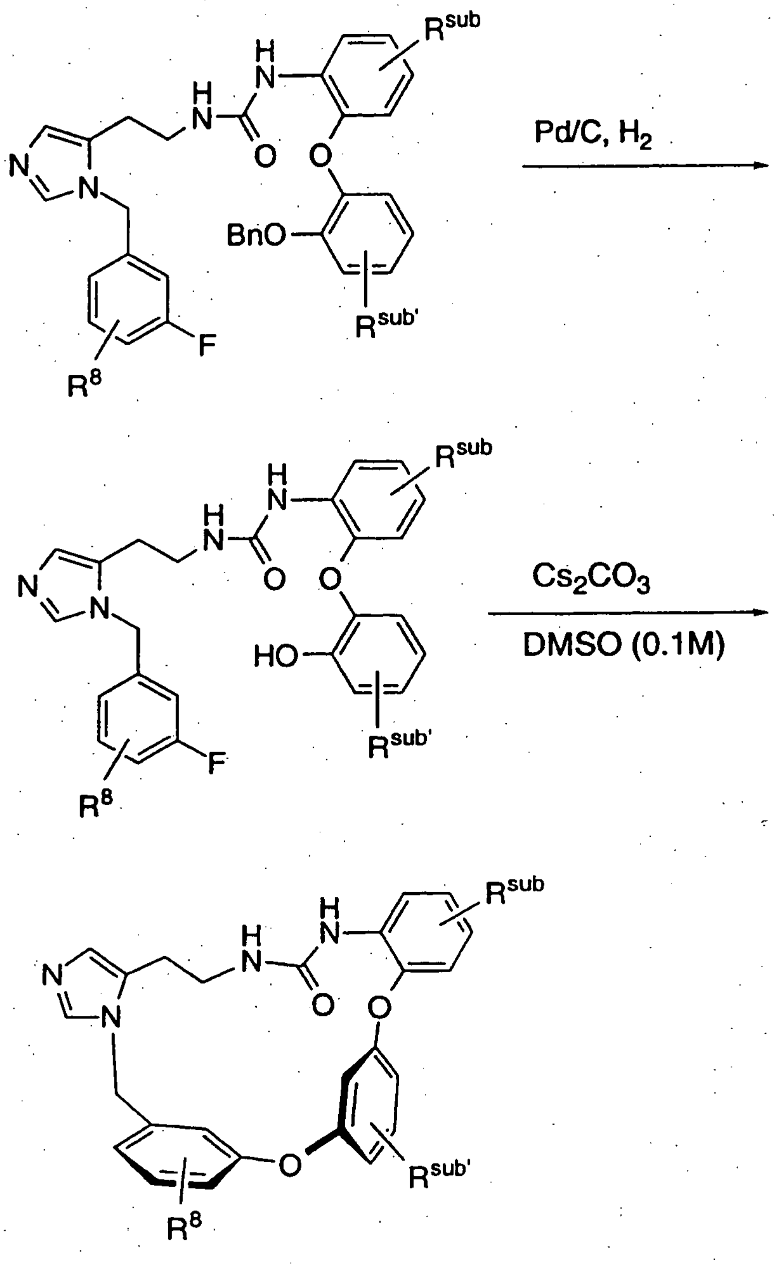
SCHEME 97 (continued)



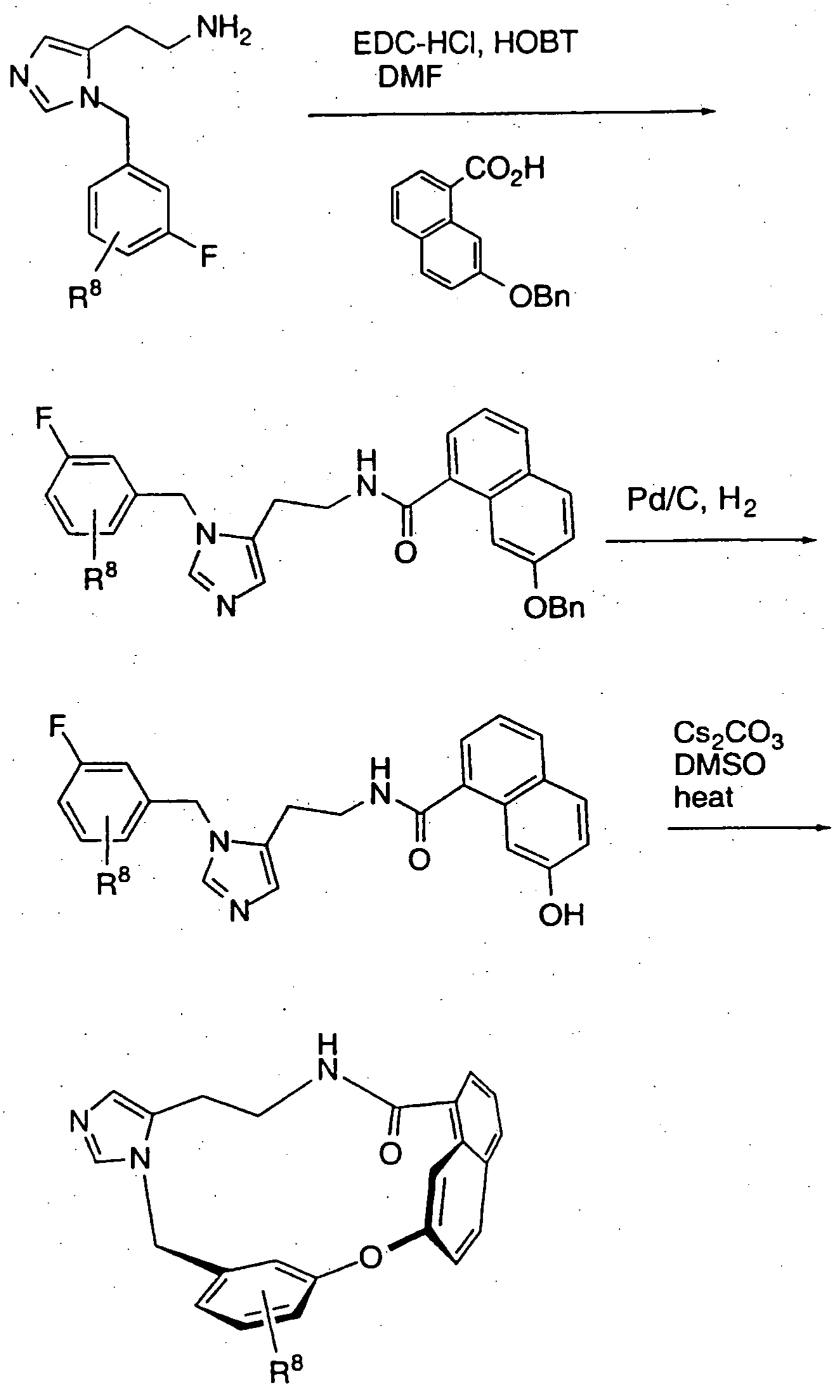
SCHEME 98


NH2
N
N
F
R8
I
O
Cl3C-O-C-O-CCl3
NCO
N
N
F
R8
H2N
Rsub
O
BnO
Rsub'
XIII
NaH
DMF
H
N
H
N
O
N
N
F
R8
Rsub
O
BnO
Rsub'

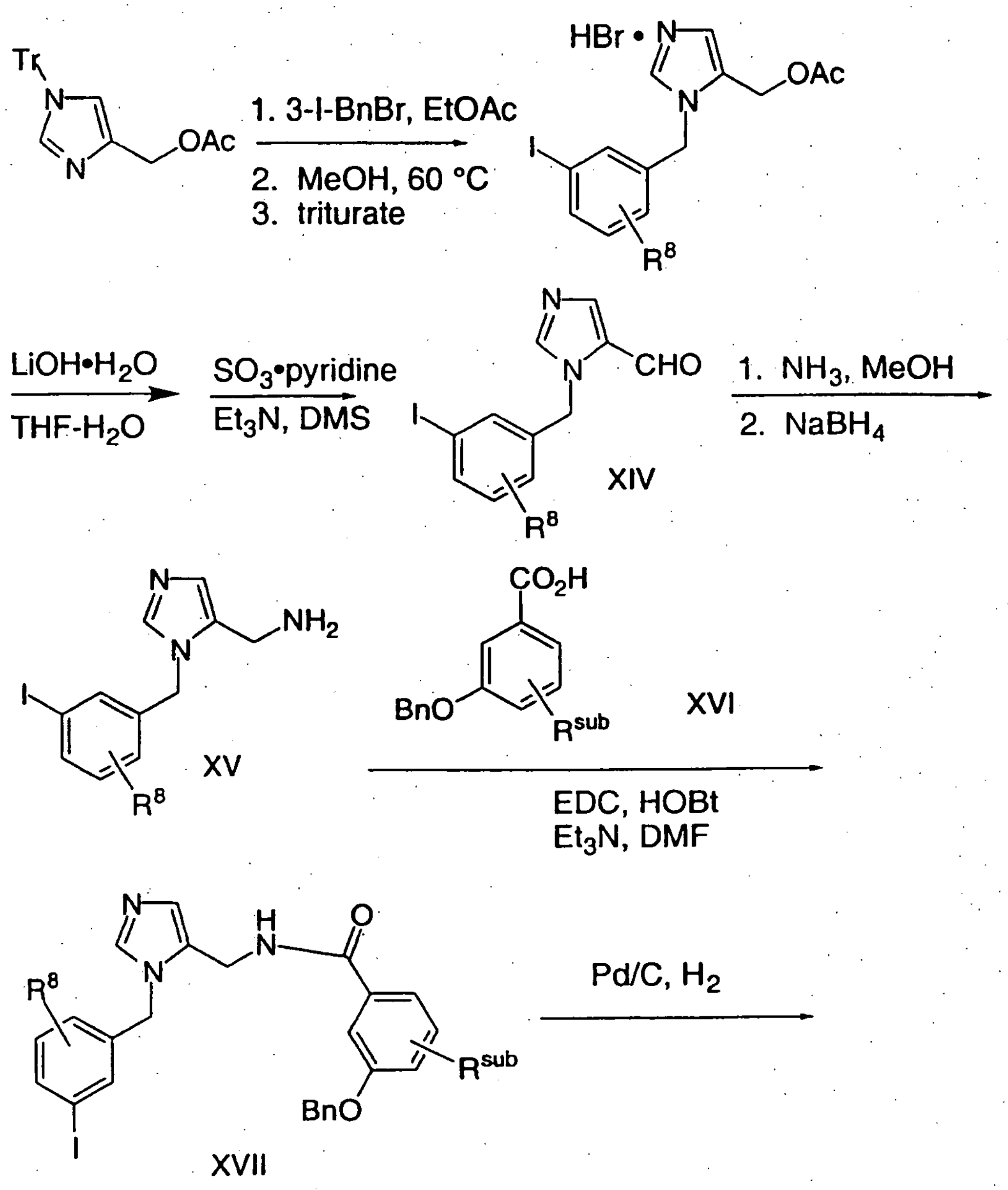
SCHEME 98 (continued)



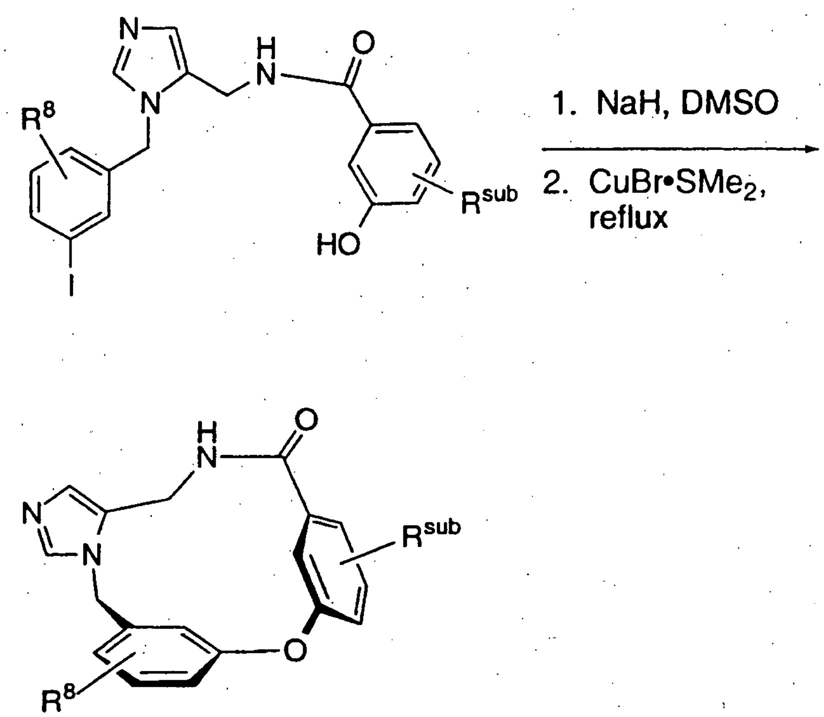
SCHEME 99


NH2
N
N
F
R8
EDC-HCl, HOBT
DMF
CO2H
OBn
F
H
N
N
R8
N
O
OBn
Pd/C, H2
F
H
N
N
R8
N
O
OH
Cs2CO3
DMSO
heat
H
N
N
N
O
O
R8

SCHEME 100


Tr
OAc
1. 3-I-BnBr, EtOAc
2. MeOH, 60 °C
3. triturate
HBr •
OAc
I
R8
LiOH•H2O
THF-H2O
SO3•pyridine
Et3N, DMS
CHO
XIV
1. NH3, MeOH
2. NaBH4
NH2
XV
CO2H
BnO
Rsub
XVI
EDC, HOBt
Et3N, DMF
H
O
Rsub
BnO
XVII
Pd/C, H2

SCHEME 100 (Continued)



XVIII

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

The standard workup referred to in the examples refers to solvent extraction and washing the organic solution with 10% citric acid, 10% sodium bicarbonate and brine as appropriate. Solutions were dried over sodium sulfate and evaporated *in vacuo* on a rotary evaporator.

EXAMPLE 1

5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-1-(2,3-dimethylphenyl)piperazin-2-one ditrifluoroacetic acid salt

Step A: N-Methoxy-N-methyl 2(S)-(*tert*-butoxycarbonylamino)-hexanamide

2(S)-(*tert*-Butoxycarbonylamino)hexanoic acid (24.6 g, 0.106 mol), N,O-dimethylhydroxylamine hydrochloride (15.5 g, 0.15 mol), EDC hydrochloride (22.3 g, 0.117 mol) and HOBT (14.3 g, 0.106 mol) were stirred in dry, degassed DMF (300 mL) at 20°C under nitrogen. N-Methylmorpholine was added to obtain pH 7. The reaction was stirred overnight, the DMF distilled under high vacuum, and the residue partitioned between ethyl acetate and 2% potassium hydrogen sulfate. The organic phase was washed with saturated sodium bicarbonate, water, and saturated brine, and dried with magnesium sulfate. The solvent was removed in vacuo to give the title compound.

Step B: 2(S)-(*tert*-Butoxycarbonylamino)hexanal

A mechanically stirred suspension of lithium aluminum hydride (5.00 g, 0.131 mol) in ether (250 mL) was cooled to -45°C under nitrogen. A solution of the product from Step A (28.3 g, 0.103 mol) in ether (125 mL) was added, maintaining the temperature below -35°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. A solution of potassium hydrogen sulfate (27.3 g, 0.200 mol) in water was slowly added, maintaining the temperature below -5°C. After quenching, the reaction was stirred at room temperature for 1h. The mixture was filtered through Celite, the ether evaporated, and the remainder partitioned between ethyl acetate and 2% potassium hydrogen sulfate. After washing with saturated brine, drying over magnesium sulfate and solvent removal, the title compound was obtained.

Step C: N-(2,3-Dimethylphenyl)-2(S)-(*tert*-butoxycarbonylamino)-hexanamine

2,3-Dimethylaniline (8.32 mL, 68.3 mmol) was dissolved in dichloroethane under nitrogen. Acetic acid was added to obtain pH 5, and sodium triacetoxyborohydride (17.2 g, 80.8 mmol) and crushed molecular sieves (4 g) were added. A solution of the product from Step B (13.3 g, 62.1 mmol) in dichloroethane (80 mL) was added slowly dropwise at 20°C. The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The aqueous layer was removed, the organic phase washed with saturated brine and dried over magnesium sulfate. Crystallization from hexane gave the title compound.

Step D: 4-*tert*-Butoxycarbonyl-5(S)-*n*-butyl-1-(2,3-dimethylphenyl)piperazin-2-one

A solution of the product from Step C (8.50 g, 26.5 mmol) in ethyl acetate (250 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (150 mL). Chloroacetyl chloride (2.33 mL, 29.1 mmol) was added, and the reaction stirred at) 0°C for 1h. The layers were separated, and the ethyl acetate phase was washed with saturated brine, and dried over magnesium sulfate. The crude product was dissolved in DMF (300 mL) and cooled to 0°C under nitrogen. Sodium hydride (1.79 g, 60% dispersion in oil, 44.9 mmol) was added portionwise to maintain moderate hydrogen evolution. After 30 min, an additional amount of sodium hydride was added (0.8 g). The reaction was stirred another 30 min, then quenched with saturated ammonium chloride. The DMF was distilled *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, saturated brine, and dried over magnesium sulfate. The crude product was chromatographed on silica gel with 20-30% ethyl acetate in hexane to obtain the title compound.

Step E: 5(S)-*n*-Butyl-1-(2,3-dimethylphenyl)-4-[4-(1-triphenylmethylimidazolyl)methyl]piperazin-2-one

A solution of the product from Step D (0.570 g, 1.58 mmol) in ethyl acetate (50 mL) was cooled to -15°C under nitrogen. HCl gas

was bubbled through for 15 min, and the reaction solution warmed to 0°C for 2h. The solvent was removed *in vacuo*, and the resulting solid was dissolved in dichloroethane (20 mL). Sodium triacetoxyborohydride (0.502 g, 2.37 mmol) and 1-triphenylmethyl-4-imidazolyl carboxaldehyde (0.534 g, 1.58 mmol) was added. The reaction was stirred overnight at 20°C then poured into saturated sodium bicarbonate solution. The organic phase was washed with saturated brine and dried over magnesium sulfate. Silica gel chromatography using 4% methanol in dichloromethane as eluant yielded the title compound.

<u>Step F:</u> <u>5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)imidazol-5-ylmethyl]-1-(2,3-dimethylphenyl)piperazin-2-one ditrifluoroacetic acid salt</u>

4-Cyanobenzylbromide (0.043 g, 0.22 mmol) was added at 20°C to a solution of 5(S)-*n*-butyl-1-(2,3-dimethylphenyl)-4-[4-(1-triphenylmethylimidazolyl)methyl]piperazin-2-one (0.120 g, 0.21 mmol) from Step E, in acetonitrile (10 mL). After 48 h, the solvent was removed *in vacuo*, and the crude product dissolved in dichloromethane (6 mL). Triethylsilane (0.13 mL) and trifluoroacetic acid (2 mL) were added, and the reaction stirred at 20°C for 2h. The volatiles were removed *in vacuo*, and the residue partitioned between hexane and water-methanol. The aqueous phase was injected onto a reverse phase preparative HPLC column and purified with a mixed gradient of 30%-60% acetonitrile/0.1% TFA; 70%-40% 0.1% aqueous TFA over 50 min. The title compound was isolated after lyophilization from water-acetonitrile solution. FAB ms (m+1) 456. Anal. Calc. for $C_{28}H_{33}N_5O \cdot 0.7\ H_2O \cdot 2.0$ TFA: C, 55.28; H, 5.13; N, 10.07. Found: C, 55.27; H, 5.20; N, 10.41.

EXAMPLE 2

<u>Preparation of (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone dihydrochloride (Compound 1)</u>

<u>Step A:</u> <u>Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole</u>

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

Step C: Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (85.8 g, 225 mmol) and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated

with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step D: Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step C (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step E: Preparation of 1-(4-cyanobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step D (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in a subsequent step (Step L) without further purification.

Step F: Preparation of (S)-2-(*tert*-butoxycarbonylamino)-*N*-(3-chlorophenyl)-3-[(triphenylmethyl)thio]-1-propanamine

To a solution of 3-chloroaniline (0.709 mL. 6.70 mmol) in 30 mL of dichloromethane at room temperature was added 1.2 g of crushed 4Å molecular sieves. Sodium triacetoxyborohydride (3.55 g, 16.7 mmol) was added, followed by dropwise addition of *N*-methylmorpholine to achieve a pH of 6.5. L-*S*-Trityl-*N*-Boc-cysteinal (3.15 g, 7.04 mmol) (prepared according to S.L. Graham et al. *J. Med. Chem.*, (1994) Vol. 37, 725-732) was added, and the solution was stirred for 48 hours. The reaction was quenched with sat. aq. $NaHCO_3$, diluted with EtOAc, and

the layers were separated. The organic material was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide an oil which was purified by silica gel chromatography (15% EtOAc/ hexane) to give the title amine.

Step G: Preparation of (S)-*N*-[2-(*tert*-butoxycarbonylamino)-3-((triphenylmethyl)thio)propyl]-2-chloro-*N*-(3-chlorophenyl)acetamide

The aniline derivative from Step F (2.77 g, 4.95 mmol) was dissolved in 73 mL of EtOAc and 73 mL of sat. $NaHCO_3$ soln., then cooled to 0 °C. With vigorous stirring, chloroacetyl chloride (0.533 mL. 6.69 mmol) was added dropwise. After 3 hours, the reaction was diluted with water and EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide crude titled chloroacetamide which was used without further purification.

Step H: Preparation of (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[*S*-(triphenylmethyl)thiomethyl]piperazin-2-one

To a solution of chloroacetamide from Step G (3.29 g crude, theoretically 4.95 mmol) in 53 mL of DMF at 0 °C was added cesium carbonate (4.84 g, 14.85 mmol). The solution was stirred for 48 hours, allowing it to warm to room temperature. The solution was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as an oil. This material was purified by silica gel chromatography (20% EtOAc/hexane) to yield the product as a white solid.

Step I: Preparation of (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-(thiomethyl)piperazin-2-one

A solution of piperazinone from Step H (625 mg, 1.04 mmol) in degassed EtOAc (38 mL) and EtOH (12 mL) was warmed to 30 °C. A solution of $AgNO_3$ (177 mg, 1.04 mmol) and pyridine (0.084 mL, 1.04 mmol) in 8 mL of EtOH was added, and the solution was heated to reflux. After 45 minutes, the reaction was concentrated *in vacuo*, then

redissolved in 26 mL of degassed EtOAc. Through this solution was bubbled H_2S gas for 2.5 minutes, then activated charcoal was added after 4 minutes. The material was filtered through celite and rinsed with degassed EtOAc, concentrated *in vacuo*, then reconcentrated from degassed CH_2Cl_2 to provide the crude product which was used without further purification.

Step J: Preparation of (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[(ethylthio)methyl]piperazin-2-one

A solution of the thiol from Step I (*ca*. 1.04 mmol) in 3 mL of THF was added *via* cannula to a suspension of NaH (51.4 mg, 60% disp. in mineral oil, 1.28 mmol) in 2 mL THF at 0°C. After 10 minutes, iodoethane was added (0.079 mL, 0.988 mmol), and the solution was stirred for 1.5 hours. The reaction was poured into EtOAc, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. This material was purified by silica gel chromatography (1% MeOH/CH_2Cl_2) to yield the titled product.

Step K: Preparation of (S)-4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-5-[(ethanesulfonyl)methyl]piperazin-2-one

To a solution of the sulfide from Step J (217 mg, 0.563 mmol) in 3 mL of MeOH at 0°C was added a solution of magnesium monoperoxyphthalate (835 mg, 1.69 mmol) in 2 mL MeOH. The reaction was stirred overnight, allowing it to warm to room temperature. The solution was cooled to 0°C, quenched by the addition of 4 mL 2N $Na_2S_2O_3$ soln., then concentrated *in vacuo*. The residue was partitioned between EtOAc and sat $NaHCO_3$ solution, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude sulfone as a white waxy solid.

Step L: Preparation of (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl]-2-piperazinone dihydrochloride

To a solution of the Boc-protected piperazinone from Step K (224 mg, 0.538 mmol) in 5 mL of dichloromethane at 0°C was added 2.5

mL of trifluoroacetic acid (TFA). After 45 minutes, the reaction was concentrated *in vacuo*, then azeotroped with benzene to remove the excess TFA. The residue was taken up in 4 mL of 1,2-dichloroethane and cooled to 0°C. To this solution was added 4Å powdered molecular sieves (340 mg), followed by sodium triacetoxyborohydride (285 mg, 1.34 mmol) and several drops of triethylamine to achieve pH = 6. The imidazole carboxaldehyde from Step E (125 mg, 0.592 mmol) was added, and the reaction was stirred at 0°C. After 2 days, the reaction was poured into EtOAc, washed with dilute aq. $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was taken up in methanol and injected onto a preparative HPLC column and purified with a mixed gradient of 15%-50% acetonitrile/0.1% TFA; 85%-50% 0.1% aqueous TFA over 60 minutes. After concentration *in vacuo*, the resultant product was partitioned between dichloromethane and aq. $NaHCO_3$ soln., and the aqueous phase was extracted with CH_2Cl_2. The organic solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness to provide the product free base, which was taken up in CH_2Cl_2 and treated with 2.1 equivalents of 1 M HCl/ether solution. After concentrated *in vacuo*, the product dihydrochloride was isolated as a white powder.

EXAMPLE 3

5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one dihydrochloride

Step A: N-(2-Methylphenyl)-2(S)-(*tert*-butoxycarbonylamino)-hexanamine

The title compound was prepared according to the procedure described in Example 1, Step C, except using *o*-toluidine (0.32 mL, 3.00 mmol), 2(S)-(*tert*-butoxycarbonylamino)hexanal (0.538, 2.50 mmol), sodium triacetoxyborohydride (0.795 g, 3.75 mmol) in dichloroethane (10 mL) The crude product was purified by column chromatography to yield the title compound.

Step B: 4-*tert*-Butoxycarbonyl-5(S)-*n*-butyl-1-(2-methylphenyl) piperazin-2-one

The title compound was prepared essentially according to the procedure described in Example 1, Step D, except using N-(2-methylphenyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine (0.506 g, 1.65 mmol), chloroacetyl chloride (0.158 mL, 1.98 mmol) in ethyl acetate-saturated sodium bicarbonate at 0°C. The crude product thus obtained was dissolved in DMF (15 mL), cooled to 0°C under nitrogen, and treated with cesium carbonate (1.61 g, 4.95 mmol). The reaction was stirred at 0°C for 2h, and at room temperature for 2h. The reaction was quenched with saturated ammonium chloride, and extracted with ethyl acetate. The extracts were dried and evaporated to give the title compound.

Step C: 5(S)-*n*-Butyl-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-1-(2-methylphenyl)piperazin-2-one dihydrochloride

The product from Step B (0.534 g, 1.50 mmol) was deprotected with trifluoroacetic acid (4 mL) in methylene chloride (10 mL). The title compound was prepared according to the procedure described in Example 1, Step E, except using 5(S)-*n*-butyl-1-(2-methylphenyl)piperazin-2-one ditrifluoroacetic acid salt, 1-(4-cyanobenzylimidazole)-5-carboxaldehyde (0.317 g, 1.50 mmol), and sodium triacetoxyborohydride (0.477 g, 2.25 mmol) in dichloroethane (15 mL). The crude product was injected onto a preparative HPLC column and purified with a mixed gradient of acetonitrile/0.1% TFA and 0.1% aqueous TFA. The pure fractions were combined and converted to the HCl salt. The title compound was obtained as a white solid. FAB ms (m+1) 442.

Anal. Calc. for $C_{27}H_{31}N_5O \cdot 2.5\ HCl \cdot 2.05\ H_2O$:

C, 56.95; H, 6.66; N, 12.30.

Found: C, 56.93; H, 5.75; N, 11.55.

EXAMPLE 4

1-(3-chloropheny)-4-[1-(4-cyanobenzyl)-2-methyl-imidazolylmethyl]-2-piperazinone dihydrochloride

Step A: 4-Bromo-2-methylimidazole-5-carboxaldehyde

4-Bromo-5-hydroxymethyl-2-methylimidazole was prepared according to the procedure described by S. P. Watson, Synthetic Communications, 22, 2971-2977 (1992). A solution of 4-bromo-5-hydroxymethyl-2-methylimidazole (4.18 g, 21.9 mmol) was refluxed with manganese dioxide (16.1 g) in 1:1 methylene chloride:dioxane (200 mL) for 16 h. The cooled reaction was filtered through celite and concentrated to yield the title compound as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.57 (1H, s), 2.52 (3H, s).

Step B: 4-Bromo-1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde

4-Cyanobenzylbromide (1.05 g, 5.39 mmol) was added to a solution of 4-bromo-2-methylimidazole-5-carboxaldehyde (1.02 g, 5.39 mmol) in dimethylacetamide (15 mL). The solution was cooled to -10°C and powdered potassium carbonate (0.745 g, 5.39 mmol) added. The reaction was stirred at -10°C for 2 h, and a further 4 h at 20°C. The reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water, saturated brine, and dried over magnesium sulfate. Solvent evaporation yielded a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (1H, s), 7.64 (2H, d, J=7 Hz) , 7.15 (2H, d, J=7Hz) 5.59 (2H, s), 2.40 (3H, s).

Step C: 1-(4-Cyanobenzyl)-2-methylimidazole-5-carboxaldehyde

A solution of 4-bromo-1-(4-cyanobenzyl)-2-methylimidazole-5-carboxaldehyde (1.33 g, 4.37 mmol) and imidazole (0.600 g, 8.74 mmol) in 1:1 ethyl acetate-alcohol (150 mL) was stirred with 10% palladium on carbon (0.020 g) under 1 atm hydrogen. After 2 h, the reaction was filtered through celite and concentated to give the title compound as a

white solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.62 (1 H, s), 7.90 (1H, s), 7.81 (2H, d, J=8 Hz), 7.20 (2H, d, J=8 Hz), 5.64 (2H, s), 2.33 (3H, s).

Step D: Preparation of N-(3-chlorophenyl)ethylenediamine hydrochloride

To a solution of 3-chloroaniline (30.0 mL, 284 mmol) in 500 mL of dichloromethane at 0°C was added dropwise a solution of 4 N HCl in 1,4-dioxane (80 mL, 320 mmol HCl). The solution was warmed to room temperature, then concentrated to dryness *in vacuo* to provide a white powder. A mixture of this powder with 2-oxazolidinone (24.6 g, 282 mmol) was heated under nitrogen atmosphere at 160°C for 10 hours, during which the solids melted, and gas evolution was observed. The reaction was allowed to cool, forming the crude diamine hydrochloride salt as a pale brown solid.

Step E: Preparation of *N*-(*tert*-butoxycarbonyl)-*N'*-(3-chlorophenyl)ethylenediamine

The amine hydrochloride from Step D (*ca.* 282 mmol, crude material prepared above) was taken up in 500 mL of THF and 500 mL of sat. aq. $NaHCO_3$ soln., cooled to 0°C, and di-*tert*-butylpyrocarbonate (61.6 g, 282 mmol) was added. After 30 h, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled carbamate as a brown oil which was used in the next step without further purification.

Step F: Preparation of *N*-[2-(*tert*-butoxycarbamoyl)ethyl]-*N*-(3-chlorophenyl)-2-chloroacetamide

A solution of the product from Step E (77 g, *ca.* 282 mmol) and triethylamine (67 mL, 480 mmol) in 500 mL of CH_2Cl_2 was cooled to 0°C. Chloroacetyl chloride (25.5 mL, 320 mmol) was added dropwise, and the reaction was maintained at 0°C with stirring. After 3 h, another portion of chloroacetyl chloride (3.0 mL) was added dropwise. After 30 min, the reaction was poured into EtOAc (2 L) and

washed with water, sat. aq. NH_4Cl soln, sat. aq. $NaHCO_3$ soln., and brine. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the chloroacetamide as a brown oil which was used in the next step without further purification.

Step G: Preparation of 4-(*tert*-butoxycarbonyl)-1-(3-chlorophenyl)-2-piperazinone

To a solution of the chloroacetamide from Step F (*ca.* 282 mmol) in 700 mL of dry DMF was added K_2CO_3 (88 g, 0.64 mol). The solution was heated in an oil bath at 70-75°C for 20 hrs., cooled to room temperature, and concentrated *in vacuo* to remove *ca.* 500 mL of DMF. The remaining material was poured into 33% EtOAc/hexane, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the product as a brown oil. This material was purified by silica gel chromatography (25-50% EtOAc/hexane) to yield pure product, along with a sample of product (ca. 65% pure by HPLC) containing a less polar impurity.

Step H: Preparation of 1-(3-chlorophenyl)-2-piperazinone hydrochloride

Through a solution of Boc-protected piperazinone from Step G (17.19 g, 55.4 mmol) in 500 mL of EtOAc at -78°C was bubbled anhydrous HCl gas. The saturated solution was warmed to 0°C, and stirred for 12 hours. Nitrogen gas was bubbled through the reaction to remove excess HCl, and the mixture was warmed to room temperature. The solution was concentrated *in vacuo* to provide the hydrochloride as a white powder.

Step I: Preparation of 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone dihydrochloride

To a solution of the amine from Step H (275 mg, 1.11 mmol) in 4 mL of 1,2-dichloroethane at 0°C was added 4Å powdered molecular sieves (0.50 g), followed by sodium triacetoxyborohydride

(370 mg, 1.75 mmol). The imidazole carboxaldehyde from Step C (249 mg, 1.11 mmol) was added, and the reaction was stirred at 0°C. After three hours, the reaction was poured into EtOAc, washed with dilute aq. $NaHCO_3$, and the aqueous layer was back-extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was taken up in 25 mL of 5:1 CH_2Cl_2:propylamine and stirred for 6 hours, then concentrated *in vacuo* to afford a pale yellow foam. This material was purified by silica gel chromatography (5-7% MeOH/CH_2Cl_2), and the resultant white foam was taken up in CH_2Cl_2 and treated with excess of 1 M HCl/ether solution. After concentrated *in vacuo*, the titled compound dihydrochloride was isolated as a white powder. FAB ms: 420.15 (M+1).

Anal. Calc for $C_{23}H_{22}ClN_5O \cdot 3.20\ HCl \cdot 0.10\ H_2O$,
C, 51.31; H, 4.76; N,13.01.
Found: C, 51.30; H, 4.74; N, 12.87.

EXAMPLE 5

Preparation of 1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Step A: Preparation of 3-(4-cyanobenzyl) histamine

N$^{\gamma}$-Pivaloyloxymethyl-N$^{\alpha}$-phthaloylhistamine (4.55 g, 12.8 mmol) was prepared as previously described (J. C. Emmett, F. H. Holloway, and J. L. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1341, (1979)). α-Bromo-p-tolunitrile (3.77 g, 19.2 mmol) was dissolved in acetonitrile (70 mL). The solution was heated at 55°C for 4 h, cooled to room temperature, and filtered to remove the white solid. The acetonitrile (30 mL) was concentrated to 1/2 its volume under reduced pressure and the solution was heated at 55°C overnight. The solution was cooled and filtered to give a white solid. The volume of the filtrate was reduced to 10 mL, the solution was heated at 55°C for 1 hr, then cooled to room temperature, diluted with EtOAc (25 mL) and filtered to

obtain additional white solid. The solids were combined, dried, and used without further purification.

1-Pivaloyloxymethyl-3-(4-cyanobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide (6.13 g, 11.1 mmol) in methanol (100 mL) was saturated with ammonia gas while the temperature was maintained below 30^{o}C. The solution was stirred for 1 hr, concentrated to dryness, and extracted with CH_2Cl_2 (3x200 mL), dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 10:90:1 MeOH/ CH_2Cl_2/NH_4OH) to give 4-cyanobenzyl-N$^{\alpha}$-phthaloylhistamine.

3-(4-Cyanobenzyl)-N$^{\alpha}$-phthaloylhistamine (1.64 g, 4.61 mmol), and hydrazine (1.46 mL, 46.1 mmol) were dissolved in absolute EtOH (70 mL). The solution was concentrated after 1 hr and filtered to remove a white precipitate which was washed several times with EtOH. The filtrate was concentrated and the residue was chromatographed (silica gel, 10:90:1 MeOH/CH_2Cl_2/NH_4OH) to give the title compound.

Step B: Preparation of 1-(2,2-Diphenylethyl)-3-carboxy piperidine

Nipecotic acid (300 mg, 2.38 mmol), diphenylacetaldehyde (1.26 mL, 7.13 mmol), sodium cyanoborohydride (448 mg, 7.13 mmol), and HOAc (204 uL, 3.57 mmol) were dissolved in MeOH (20 mL) and stirred at ambient temperature overnight. The solution was concentrated under reduced pressure, take up in ether and 1N NaOH, extract with ether (3X), acidify the aqueous layer with 1N HCl, and extract with EtOAc (3X). The EtOAc layers were dried ($MgSO_4$) and concentrated to give the title compound without further purification.

Step C: Preparation of 1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-3-carboxy piperidine(472 mg, 1,52 mmol), 3-(4-cyanobenzyl) histamine (456 mg, 1.52 mmol) (Step A) HOBT (216 mg, 1.60 mmol), EDC (307 mg, 1.60 mmol), and Et_3N (637 uL, 4.57 mmol) were dissolved in DMF (10 mL) and was stirred overnight at ambient temperature. The solution was concentrated under reduced pressure and chromatographed (silica gel, 0.5-2% MeOH/CH_2Cl_2 with

NH_4OH) to give the title compound ^1H NMR ($CDCl_3$) δ 7.96 (br s, 1H), 7.60 d, 2H, J=8 Hz), 7.46 (s, 1H), 7.09-7.37 (m, 12H), 6,74 (s, 1H), 5.20 (s, 2H), 4.26 (t, 1H, J=8 Hz), 3.05-3.17 (m, 2H), 2.93-3.04 (m,1H), 2.78-2.91 (m,2H), 2.49-2,61 (m 1H), 22.40-2.47 (m, 1H), 2.15-2.30 (m, 2H), 1.95-2.14 (m, 2H), 1.86 (d, 1H, J=12 Hz), 1.29-1.55 (m, 3H). FAB MS 518 (M+1)

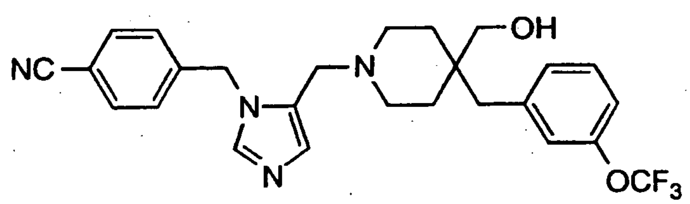
Anal. calculated for $C_{33}H_{35}N_5O_1$• 0.35 $CHCl_3$• 0.10 H_2O:

C, 71.37; H, 6.38; N, 12.48;

Found: C, 71.41; H, 6.32; N, 12.36.

EXAMPLE 6

Preparation of 4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile



Step A: Preparation of Ethyl N-tert-butoxycarbonylpiperidine-4-carboxylate

To a cold (0°C) solution of ethyl isonipecotate (39.5g, 0.251 mol) and triethylamine (38.5 mL, 0.276 mol) in dichloromethane (350 mL), a solution of di-tert-butyl dicarbonate (55.9 g, 0.256 mol) in dichloromethane (50 mL) was added over a period of 30 min. The reacting mixture was stirred at room temp. overnight. The product mixture was washed with aqueous potassium hydrogen sulfate (3 times), and brine (to pH 7). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the title compound as clear, colorless, viscous oil.

Step B: Preparation of Ethyl N-tert-butoxycarbonyl-4-(3-trifluoro-methoxybenzyl)piperidine-4-carboxylate

To a cold (-78°C) solution of ethyl N-tert-butoxycarbonyl-piperidine-4-carboxylate (5.16 g, 20.05 mmol) in anhydrous tetrahydrofuran (60 mL), a solution of sodium bis(trimethylsilyl)amide (28 mL, 1M, 28 mmol) was added over a period of 30 min. The resultant mixture was stirred at -78 °C for 1 h, and 3-(trifluoromethoxy)benzyl bromide (5.90 g, 23.14 mmol) was added. The reacting mixture was allowed to warm to room temp. and stirred overnight. The product mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 20% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title compound.

<u>Step C</u>: <u>Preparation of N-tert-butoxycarbonyl-4-(3-trifluoro-methoxybenzyl)-4-hydroxymethylpiperidine</u>

To a slurry of lithium aluminum hydride (585 mg, 15.4 mmol) in anhydrous diethyl ether (100 mL) at 0 °C, a solution of ethyl N-tert-butoxycarbonyl-4-(3-trifluoromethoxybenzyl)piperidine-4-carboxylate (5.84 g, 14.0 mmol) in diethyl ether (30 mL) was added dropwise with the temp. of the reacting mixture maintained below 10 °C. The resulting mixture was stirred at 0 °C for 30 min, and quenched with successive addition of water (0.58 mL), 15% aqueous NaOH (0.58 mL), and water (1.74 mL). The resultant slurry was stirred at room temp. for 30 min., and filtered through a small plug of Celite. The filtrate was washed brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide the title alcohol.

<u>Step D</u>: <u>Preparation of 4-(3-trifluoromethoxybenzyl)-4-hydroxy-methylpiperidine hydrochloride salt</u>

A solution of N-tert-butoxycarbonyl-4-(3-trifluoromethoxy-benzyl)-4-hydroxymethylpiperidine (2.9 g) in dichloromethane (100 mL) at 0°C was saturated with hydrogen chloride gas. The resultant solution was sealed with a rubber septum and stirred at room temp. for 2.5 h.

The product solution was concentrated under vacuum to provide the title compound.

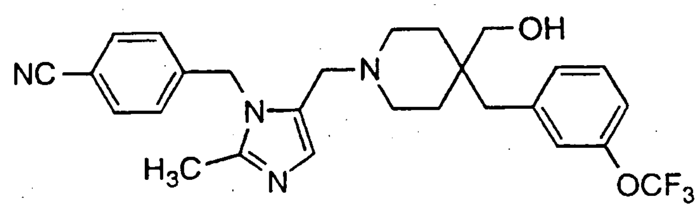
Step E. Preparation of 4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}-benzonitrile

A mixture of 4-(3-trifluoromethoxybenzyl)-4-hydroxymethylpiperidine hydrochloride salt (0.62 g, 2.0 mmol), 1-(4-cyanobenzyl)imidazole-5-carboxyaldehyde (0.45 g, 2.0 mmol; Example 1, Step E), diisopropylethylamine (0.53 mL, 3.04 mmol), anhydrous magnesium sulfate (650 mg), activated molecular sieves 3 A powder (750 mg), and anhydrous methanol (6 mL) was stirred at room temp. overnight. The pH of the mixture was adjusted to ~5 with addition of glacial acetic acid. To the mixture, a solution of sodium cyanoborohydride in THF (2.2 mL, 1 M, 2.2 mmol) was added slowly over a period of 8 h with a syringe pump, and stirred at room temp. overnight. The product mixture was diluted with chloroform, filtered through Celite. The filtrate was washed with aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 5-10% methanol in chloroform gradient. Collection and concentration of appropriate fractions provided the title compound as white solid.

Anal. Calcd for $C_{26}H_{27}N_4O_2F_3 \bullet 0.38\ H_2O$:
C, 63.56; H, 5.69; N, 11.40.
Found: C, 63.55; H, 5.72; N, 11.46.

EXAMPLE 7

Preparation of 4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile



Step A: Preparation of 1-(4-cyanobenzyl)-2-methylimidazole-5-carboxyaldehyde

To a cold (0°C) mixture of 4-formyl-2-methylimidazole (10.0 g, 91 mmol), cesium carbonate (44.4 g, 136 mmol), dimethyl formamide (300 mL) stirred with a mechanical stirred, solid 4-cyanobenzyl bromide (18.7 g, 95 mmol) was added slowly over a period of 5 h using an open end plastic syringe and a syringe pump. The resultant mixture was stirred at 0°C overnight, concentrated under vacuum. The residue was partitioned between water and ethyl acetate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was subjected to column chromatography on silica gel eluting with 4% methanol in chloroform. Collection and concentration of appropriate fractions provided the title compound as white solid.

^{1}H NMR (CDCl$_3$ 300MHz) δ 9.67 (1H, s), 7.79 (1H, s), 7.63 (2H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.6 Hz), 5,62 (2H, s), and 2.42 (3H, s) ppm.

Step B: Preparation of 4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

The title compound was prepared as white solid using the protocol described in Example 6 - Step E, substituting 1-(4-cyano-benzyl) imidazole-5-carboxyaldehyde with 1-(4-cyanobenzyl)-2-methylimidazole-5-carboxyaldehyde.

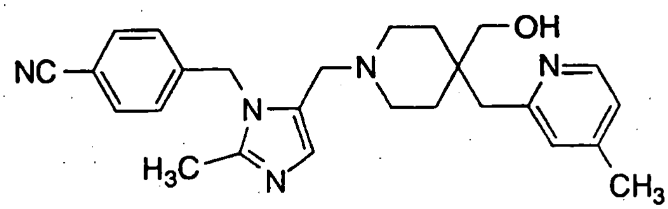
Anal. Calcd for $C_{27}H_{29}N_4O_2F_3$:

C, 62.05; H, 5.86; N, 11.24.

Found: C, 65.06; H, 5.97; N, 11.51.

EXAMPLE 8

Preparation of 4-{5-[4-Hydroxymethyl-4-(4-methylpyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile



Step A: Preparation of 2-Hydroxymethyl-4-methylpyridine

A mixture of 2,4-dimethylpyridine N-oxide (10.9 g, 88.5 mmol) and trifluoroacetic anhydride (31 mL, 219 mmol) in dichloromethane (75 mL) was stirred at room temp. overnight. The product mixture was concentrated under vacuum. The residue was dissolved in a mixture of dichloromethane (75 mL) and aqueous sodium carbonate (225 mL, 2M), and stirred vigorously for 4 h. The resultant mixture was diluted with dichloromethane. The organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 1-2% methanol in chloroform gradient. Collection and concentration of appropriate fractions provided 2-hydroxymethyl-4-methylpyridine as clear oil.

Step B: Preparation of 2-Chloromethyl-4-methylpyridine

A mixture of 2-hydroxymethyl-4-methylpyridine (5.48 g, 44.5 mmol) and thionyl chloride (60 mL, 822 mmol) in benzene (150 mL) was stirred at room temp. overnight. The product mixture was concentrated under vacuum. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The organic extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum to provide the title compound as oil. This alkylating reagent was passed through a small plug of activated basic alumina immediately before use.

Step C: Preparation of Ethyl N-tert-butoxycarbonyl-4-(4-methylpyridin-2-ylmethyl)piperidine-4-carboxylate

To a cold (-78 °C) solution of ethyl N-tert-butoxycarbonyl-piperidine-4-carboxylate (5.1 g, 19.8 mmol; Example 6, Step A) in

anhydrous THF (50 mL), a solution of solution of sodium bis(trimethylsilyl)amide (20 mL, 1M, 20 mmol) was added over a period of 15 min. The resultant mixture was stirred at -78 °C for 1 h., and 2-chloromethyl-4-methylpyridine (3.5 g, 24.7 mmol) was added. The reacting mixture was allowed to warm to room temp. and stirred overnight. The product mixture was diluted with dichloromethane was washed with brine. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 25-40% ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the title compound.

<u>Step D</u>: Preparation of <u>N-tert-Butoxycarbonyl-4-(4-methylpyridin-2-ylmethyl)-4-hydroxymethylpiperidine</u>

To a slurry of lithium aluminum hydride (280 mg, 7.37 mmol) in anhydrous diethyl ether (30 mL) at 0°C, a solution of ethyl N-tert-butoxycarbonyl-4-(4-methylpyridin-2-ylmethyl)piperidine-4-carboxylate (2.7 g, 7.45 mmol) in diethyl ether (20 mL) was added dropwise with the temperature of the reacting mixture maintained below 10°C. The resulting mixture was stirred at 0°C for 30 min, and quenched with successive addition of water (0.28 mL), 15% aqueous NaOH (0.28 mL), and water (0.84 mL). The resultant slurry was stirred at room temp. for 30 min., and filtered through a small plug of Celite. The filtrate was washed brine, dried over anhydrous magnesium sulfate, and filtered. Concentration of the filtrate under vacuum provided the title alcohol.

<u>Step E</u>: Preparation of <u>4-(4-methylpyridin-2-ylmethyl)-4-hydroxymethylpiperidine hydrochloride salt</u>

A solution of N-tert-butoxycarbonyl-4-(4-methylpyridin-2-ylmethyl)-4-hydroxymethylpiperidine (1.8 g) in dichloromethane (100 mL) at 0°C was saturated with hydrogen chloride gas. The resultant solution was sealed with a rubber septum and stirred at room temp. for 2.5 h. The product solution was concentrated under vacuum to provide the title compound.

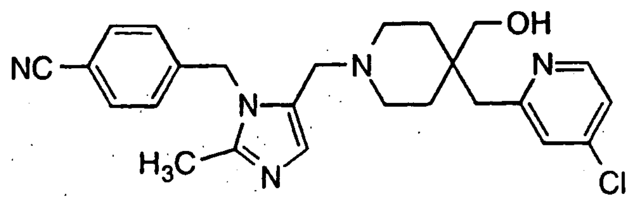
Step F: Preparation of 4-{5-[4-Hydroxymethyl-4-(4-methylpyridin-2-ylmethyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

A mixture of 4-(4-methylpyridin-2-ylmethyl)-4-hydroxymethylpiperidine hydrochloride salt (0.39 g, 1.3 mmol), 1-(4-cyanobenzyl)-2-methylimidazole-5-carboxyaldehyde (0.33 g, 1.5 mol; Example 31, Step A), diisopropylethylamine (0.57 mL, 3.25 mmol), anhydrous magnesium sulfate (0.55 g), activated molecular sieves 3 A powder (0.55 g), and anhydrous methanol (3.5 mL) was stirred at room temp. overnight. The pH of the mixture was adjusted to ~5 with addition of glacial acetic acid. To the this mixture, a solution of sodium cyanoborohydride in THF (1.35 mL, 1 M, 1.35 mmol) was added slowly over a period of 8 h with a syringe pump, and stirred at room temp. overnight. The product mixture was diluted with chloroform, filtered through Celite. The filtrate was washed with aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 5% methanol in chloroform. Collection and concentration of appropriate fractions provided a gum, which was triturated with anhydrous diethyl ether to provide the title compound as white solid.

Anal. Calcd for $C_{26}H_{31}N_5O$:
C, 72.70; H, 7.27; N, 16.30.
Found: C, 72.52; H, 7.08; N, 16.18.

EXAMPLE 9

Preparation of 4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile



Step A: Preparation of 2-Chloromethyl-4-chloropyridine

To a slurry of lithium aluminum hydride (0.45 g, 11.9 mmol) in anhydrous diethyl ether (40 mL) at 0°C, a solution of methyl 4-chloro-pyridine-2-carboxylate (2.0 g, 11.7 mmol) in diethyl ether (30 mL) was added. The resulting mixture was stirred at room temp. overnight, and quenched with successive addition of water (0.45 mL), 15% aqueous NaOH (0.45 mL), and water (1.35 mL). The resultant slurry was stirred at room temp. for 30 min., and filtered through a small plug of Celite. The filtrate was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to provide 4-chloro-2-hydroxymethylpyridine.

The title compound was prepared using the protocol described in Example 8, Step B substituting 2-hydroxymethyl-4-methylpyridine with 4-chloro-2-hydroxymethylpyridine.

Step B: Preparation of 4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

The title compound was prepared using the protocol described in Example 8, Step C - F substituting 2-chloromethyl-4-methylpyridine with 2-chloromethyl-4-chloropyridine in Step C.

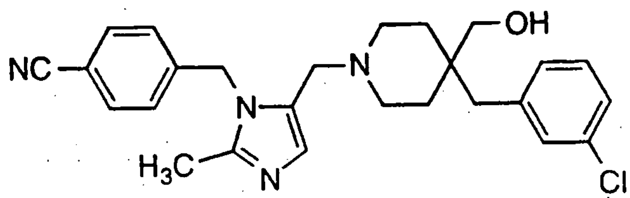
Anal. Calcd for $C_{25}H_{28}N_5OCl$:

C, 66.73; H, 6.27; N, 15.56.

Found: C, 66.52; H, 6.19; N, 15.35.

EXAMPLE 10

Preparation of 4-{5-[4-Hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile



The title compound was prepared as white solid according to the procedure described in Example 6, Step B - E substituting 3-(trifluoromethoxy)benzyl bromide with 3-chlorobenzyl bromide in Step B, and substituting 1-(4-cyanobenzyl)imidazole-5-carboxyaldehyde with 1-(4-cyanobenzyl)-2-methylimidazole-5-carboxyaldehyde (Example 7, Step A) in Step E.

Anal. Calcd. for $C_{26}H_{29}N_4OCl \bullet 0.20\ H_2O$:
C, 69.00; H, 6.55; N, 12.38.
Found: C, 68.96; H, 6.78; N, 12.49.

EXAMPLE 11

4-{3-[4-(-2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

Step 1: 4-Iodobenzyl alcohol

Methyl 4-iodobenzoate (5g, 19.07 mmol) was suspended in THF (100 mL). $LiBH_4$ (40 mmol) was added slowly, via syringe. Reaction mixture was heated to 60°C for 4 days. 1N HCl was added slowly. Reaction mixture was stirred for 1/2 hour then was extracted 3 times with EtOAc. The organic layers were combined, washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated to give 4-iodobenzyl alcohol as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H); 7.11 (d, 2H); 4.71 (d, 2H); 1.65 (t, 1H)

Step 2: 4-(-2-Oxo-2-H-pyridin-1-yl)benzyl alcohol

2-Hydroxypyridine (10.0 mmol; 956 mg) ,4-iodobenzyl alcohol (17.09 mmol, 4.0g), K_2CO_3 (11.0 mmol, 1.52 g), and copper (0.2 mmol, 15 mg) were mixed under argon and heated to 150°C for 16 hours. The solid was partitioned between saturated $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was back extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to yield a yellow oil which was purified by flash chromatography (EtOAc) to give pure the title compound as a crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2H); 7.43-7.41 (m, 4H); 6.68-6.65 (d, 1H): 6.27-6.23 (t, 1H); 4.75-4.75(d, 2H); 1.96-1.95 (bt, 1H).

Step 3: 4-(-2-Oxo-2-H-pyridin-1-yl)benzyl bromide

A solution of NBS (1.59g, 8.94 mmol) and CH_2Cl_2 was cooled to 0°C. To this solution (under Ar) was added Me_2S (10.72 mmol, 0.78 mL) via syringe. This mixture was then cooled to -20°C and added to a solution of the benzyl alcohol from Step 2 (1.2g, 5.96 mmol) in CH_2Cl_2 via pipette. The reaction mixture was warmed to 0°C and stirred for several hours. The residue was poured into ice water and extracted with CH_2Cl_2 (3x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to give the title compound as a yellow solid, which will be used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (d, 2H); 7.37-7.31 (m, 4H); 6.67 (d, 1H); 6.25 (t, 1H); 4.52 (s, 2H).

Step 4: 4-(1-Trityl-1H-imidazol-4-ylmethyl)-benzonitrile

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon for 45 minutes, at 20°C. The suspension was cooled to 0°C and α-bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenylphosphine) Nickel II chloride (2.40g, 3.64 mmol) and 5-iodotrityl imidazole (15.95g,

36.6 mmol) were added in one portion. The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of saturated NH_4Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. $NaHCO_3$ solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 0-20% EtOAc in CH_2Cl_2) to afford the title compound as a white solid. ^1H NMR ($CDCl_3$, 400Mz) δ (7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

Step 5: 4-{3-[4-(2-Oxo-2-H-pyridin-1-yl)benzyl]-3-H-imidazol-4-ylmethyl]benzonitrile

4-(-2-Oxo-2-H-pyridin-1-yl)benzyl bromide from Step 3 (1.7 mmol, 450 mg) and 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile (1.7mmol) were suspended in CH_3CN and heated to reflux for 3 hours. The reaction mixture was concentrated and the residue taken up in MeOH and refluxed for 2 hours. The MeOH was removed in-vacuo. The resulting oil was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield an oil which was purified by flash chromatography using 5% IPA/$CHCl_3$ saturated with NH_3 as an eluent. Pure fractions were collected and concentrated to give a white solid. The solids were washed with warm 50% EtOAc/Hexane and collected on a frit. The white solid was collected and dried under high vacuum at 50°C for 12 hours to give the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 3H); 7.42-7.40 (m, 1H); 7.39 (d, 2H); 7.27 (s, 1H); 7.20 (d, 2H); 7.04 (d, 2H); 6.67 (d, 1H); 6.27 (t, 1H); 4.97 (s, 2H); 3.89 (s, 2H).

EXAMPLE 12

4-{3-[4-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-imidazol-2-ylmethyl]-benzonitrile (Compound 2)

Step 1: 5-Chloro-5'-methyl-[1,2']bipyridinyl-2-one

5-Chloro-2-pyridinol (2.26g, 17.4 mmol), 2-bromo-5-methylpyridine (3.00g, 17.4 mmol), copper (0.022g, 0.35 mmol) and K_2CO_3 (2.66g, 19.2 mmol) were heated at 180°C for 16 hrs. The brown reaction mixture was cooled, diluted with EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, EtOAc: CH_2Cl_2 20:80 to 50:50 gradient elution) to afford the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.96(d, J=3.0Hz, 1H), 7.83 (d, J=8.4Hz, 1H), 7.65(dd, J=2.4 and 8.2Hz, 1H), 7.32(dd, J=2.9 and 9.7 Hz, 1H), 6.61(d, J=9.7Hz, 1H) and 2.39(s,3H)ppm.

Step 2: 5'-Bromomethyl-5-chloro-[1,2']bipyridinyl-2-one

A solution of the pyridine from Step 1(1.00g, 4.53 mmol), N-bromosuccinimide (0.81g, 4.53 mmol) and AIBN (0.030g, 0.18 mmol) in CCl_4 (40mL) was heated at reflux for 2 hrs. The solids were filtered and the filtrate collected. The solvent was evaporated in vacuo and the residue chromatographed (silica gel, EtOAc: CH_2Cl_2 25:75 to 50:50 gradient elution) to afford the title bromide.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.04(d, J= 2.9 Hz, 1H), 8.01 (d, J=8.4Hz, 1H), 7.88 (dd, J=2.4 and 8.6Hz, 1H), 7.34(dd, J= 2.9 and 9.8Hz, 1H), 6.61(d, J=9.9Hz, 1H) and 4.51 (s,2H) ppm.

Step 3: 4-{3-[4-(5-Chloro-2-oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-imidazol-2-ylmethyl]-benzonitrile hydrochloride

The bromide from Step 2 (0.750g, 2.50 mmol) and the 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile (1.06g, 2.50 mmol) in CH_3CN (10 mL) were heated at 60°C. The reaction was cooled to room temperature and the solids collected by filtration and washed with EtOAc (10mL). The solid was suspended in methanol (50 mL) and heated at reflux for 1 hr, cooled and the solvent evaporated in vacuo. The sticky residue was stirred in EtOAc (40mL) for 4 hrs and the resulting solid hydrobromide salt collected by filtration and washed with EtOAc

(40mL) and dried in vacuo. The hydrobromide salt was partitioned between sat. $NaHCO_3$ and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 4:96 to 5:95 gradient elution) to afford the free base which was converted to the hydrochloride salt to afford the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.35 (s, 1H), 8.03(d, J=2.9Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.76 (dd, J=2.4 and 9.6Hz, 1H), 7.68-7.58 (m, 3H), 7.48 (s, 1H), 7.31(d, J=8.6Hz, 2H), 6.68 (d, J=9.3Hz, 1H), 5.53 (s, 2H) and 4.24 (s, 2H) ppm.

Analysis: % Calc for $C_{22}H_{16}N_5OCl$. 1.75 HCl, 0.15 EtOAc
C 56.69, H 3.99, N 14.62
% Found: C 56.72, H 4.05, N 14.54

EXAMPLE 13

4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-imidazol-2-ylmethyl]-benzonitrile

Step 1: 5'-Methyl-[1,2']bipyridinyl-2-one

2-Pyridinone (1.00g, 10.5 mmol), 2-bromo-5-methyl-pyridine (1.81g, 10.5 mmol), Copper (0.013g, 0.20 mmol) and K_2CO_3 (1.60g, 11.6 mmol) were heated at 180°C for 16 hrs. The brown reaction mixture was cooled, diluted with EtOAc and washed with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, EtOAc as eluent) to afford the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (brs, 1H), 7.86-7.78(m,2H), 7.64(dd, J=2.3 and 8.3Hz, 1H), 7.38(m, 1H), 6.63(d, J=9.2Hz, 1H), 6.27(dt, J=1.3 and 7.0Hz, 1H) and 2.39(s,3H)ppm.

Step 2: 5'-Bromomethyl-[1,2']bipyridinyl-2-one

A solution of the pyridine from Step 1 (0.10g, 0.537

mmol), N-bromosuccinimide (0.096g, 0.537 mmol) and AIBN ((0.005g, 0.027mmol) in CCl_4 (4 mL) was heated at reflux for 2 hrs. The solvent was evaporated in vacuo and the residue was chromatographed (silica gel, EtOAc: CH_2Cl_2 25:75 to 50:50 gradient elution) to afford the title bromide.
^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (brs, 1H), 8.04(dd, J=8.4 and 2.3 Hz, 1H), 7.87 (m, 1H), 7.77(d, J= 8.3Hz, 1H), 7.61(m, 1H), 6.62(d, J=9.7Hz, 1H), 6.49 (dt, J=1.3 and 7.0Hz, 1H) and 4.68 (s,2H) ppm.

Step 3: 4-[1-(2-Oxo-2H-[1,2']bipyridinyl-5'-ylmethyl)-1H-imidazol-2-ylmethyl]-benzonitrile

The bromide from Step 2 (0.151g, 0.565 mmol) and the 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile (0.241g, 0.565 mmol) in CH_3CN (3mL) were heated at 60°C. After 18 hr methanol (4mL) was added and the reaction was heated at reflux for 2 hrs, cooled and the solvent evaporated in vacuo. The residue was partitioned between sat. $NaHCO_3$ and CH_2Cl_2 and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, MeOH: CH_2Cl_2 2:98 to 5:95 gradient elution) to afford the free base which was converted to the hydrochloride salt to afford the title compound as a white solid.
^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (s, 1H), 8.34(s, 1H), 7.88-7.70 (m, 3H), 7.67-7.56 (m, 3H), 7.47 (s, 1H), 7.30 (d, J=8.2Hz, 2H), 6.64 (d, J=9.3Hz, 1H), 6.52(t, J=6.6Hz, 1H), 5.55(s, 2H) and 4.26 (s, 2H) ppm.

Analysis: % Calc for $C_{22}H_{17}N_5O$. 1.70HCl
C 61.39, H 4.39, N 16.31
% Found: C 61.42, H 4.61, N 16.58

EXAMPLE 14

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile

Step 1: 4-Hydroxymethyl-1H-pyridin-2-one

2-Oxo-1,2-dihydropyridine-4-carboxylic acid methyl ester (1.8g, 12.2 mmol) , prepared as described in *J. Org. Chem.*, 26, 428 (1961), was suspended in THF(100ml). A small amount of DMF was added to help increase solubility. $LiBH_4$ (61 mmol) was added and the reaction was stirred for 18 hours at room temperature. MeOH and H_2O are added to quench the reaction. The reaction is then concentrated to yield a yellow oil. Flash chromatography (5% MeOH/$CHCl_3$ to 20% MeOH/$CHCl_3$) yielded 4-hydroxymethyl-1H-pyridin-2-one as a white solid.
^1H NMR (400 MHz, CD_3OD) δ 7.38-7.36 (1H,d); 6.56 (s, 1H); 6.37-6.36 (d, 1H); 4.50 s, 2H).

<u>Step 2</u>: <u>4-(tert-butyldimethylsilyloxymethyl)-1H-pyridin-2-one</u>

4-Hydroxymethyl-1H-pyridin-2-one from Step 1 (1.3g, 10.5 mmol) was dissolved in DMF. t-Butyl dimethylsilyl chloride (12.6 mmol, 1.9g) and imidazole (12.6 mmol, 858 mg) were added and the reaction was stirred for 16 hours. The reaction mixture was diluted with EtOAc and washed with H_2O (2x) and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to yield a yellow oil. Flash chromatography (EtOAC) yielded 4-(tert-butyldimethylsilyloxy-methyl)-1H-pyridin-2-one as an off white solid.
^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (d, 1H); 6.60 (s, 1H); 6.20-6.18 (d, 1H); 4.58 (s, 2H); 0.955 (s, 9H); 0.11 (s, 6H).

<u>Step 3</u>: <u>4-(tert-butyl-dimethyl-silanyloxymethyl)-1-phenyl-1H-pyridin-2-one</u>

4-(Tert-butyldimethylsilyloxymethyl)-1H-pyridin-2-one from Step 2 (1.5g, 6.3 mmol) was dissolved in iodobenzene (189 mmol, 21.12 mL) and treated with copper (6.3 mmol, 400 mg) and K_2CO_3 (6.93 mmol, 958 mg.). The brown slurry was heated to 180° for 16 hrs. The reaction mixture was cooled, diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The aqueous layer was back extracted with $CHCl_3$ (2x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield a yellow oil. Flash Chromatography (20% EtOAc/Hexane) yielded 4-(tert-butyl-dimethyl-silanyloxymethyl)-

1-phenyl-1H-pyridin-2-one as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H); 7.43-7.39 (m, 3H); 7.29-7.28 (d, 2H); 6.65 (s, 1H); 6.19 (d, 2H); 4.59 (s, 2H); 0.97 (s, 9H); 0.14 (s, 6H).

<u>Step 4</u>: <u>4-Hydroxymethyl-1-phenyl-1H-pyridin-2-one</u>

4-(Tert-butyl-dimethyl-silyloxymethyl)-1-phenyl-1H-pyridin-2-one from Step 3 (1.3g) was dissolved in TBAF in 1M THF (15 mL). The clear reaction mixture was stirred for 16 hours. The reaction mixture was concentrated and purified on a column of silica eluting with 10% MeOH/EtOAc to yield 4-hydroxymethyl-1-phenyl-1H-pyridin-2-one as a tan solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5-7.47 (m, 2H); 7.43 (d, 1H); 7.38-7.36 (m, 2H); 7.32-7.30 (d, 1H) 6.67 (s, 1H); 6.23 (d, 1H) 4.57 (d, 2H).

<u>Step 5</u>: <u>4-Bromomethyl-1-phenyl-1H-pyridin-2-one</u>

4-Hydroxymethyl-1-phenyl-1H-pyridin-2-one from Step 4 (1.0g, 5 mmol) was dissolved in CH_2Cl_2. CBr_4 (6 mmol, 2g) was added and the reaction mixture was cooled to 0°C. PPh_3 (6 mmol, 2.0 g) was added dropwise in CH_2Cl_2. The reaction mixture was stirred at 0°C for 15 minutes and then warmed to room temperature. The reaction mixture was concentrated and purified on a column of silica eluting with (30 % EtOAc /hexane to 50% EtOAc/hexane) to give 4-bromomethyl-1-phenyl-1H-pyridin-2-one (8 ,x=H) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H); 7.45-7.43 (d, 1H); 7.38-7.33 (m, 3H); 6.64 (s, 1H); 6.30-6.28 (d, 1H); 4.25 (d, 2H).

<u>Step 6</u>: <u>4-(1-Trityl-1H-imidazol-4-ylmethyl)-benzonitrile</u>

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon for 45 minutes, at 20°C. The suspension was cooled to 0°C and α-bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenylphosphine) Nickel II chloride (2.40g, 3.64 mmol) and 5-iodotrityl imidazole (15.95g, 36.6 mmol) were added in one portion. The resulting mixture was

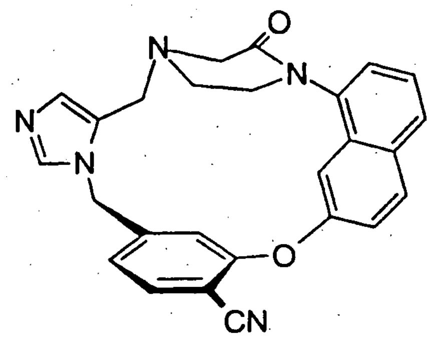
stirred 16 hours at 20°C and then quenched by addition of saturated NH_4Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. $NaHCO_3$ solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed (silica gel, 0-20% EtOAc in CH2Cl2) to afford the title compound as a white solid. ^1H NMR ($CDCl_3$, 400Mz) δ (7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

Step 7: 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride

4-Bromomethyl-1-phenyl-1H-pyridin-2-one from Step 5 (1.1g, 4.1 mmol) and 4-(1-trityl-1H-imidazol-4-ylmethyl)-benzonitrile from Step 6 (4.1 mmol, 1.7g) were suspended in CH_3CN and heated to 80°C. After 30 minutes the reaction became homogeneous. The reaction mixture was heated to 80°C for 16 hours. The heterogeneous reaction mixture was concentrated, taken up in MeOH and refluxed for 1 hour. The reaction mixture was cooled, diluted with $CHCl_3$ and washed with saturated $NaHCO_3$. The aqueous layer was back extracted 4 times with $CHCl_3$. The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to yield a yellow solid which was purified by flash chromatography (7% i-PrOH/$CHCl_3$ saturated with NH_3). Purest fractions were collected and concentrated to yield a white solid which was triturated with EtOAc. The solids were filtered, washed with EtOAc and dried under hi-vacuum for 16 hours to yield 4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl]benzonitrile, hydrochloride as a white solid.
^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H); 7.58-757 (d, 2H) 7.52-7.49 (m, 2H); 7.46-7.44 (d, 1H); 7.34-7.32 (d, 2H); 7.26-7.25 (m, 2H); 6.97 (s, 1H); 6.20 (s, 1H); 5.77 (d, 1H); 4.77 (d, 2H); 3.96 (s, 2H).

EXAMPLE 15

Preparation of (±)-19,20-Dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile (6), dihydrochloride



6

Step A: Preparation of N-(7-hydroxy-1-naphthyl)-2-[(2-(hydroxy)ethyl)amino]acetamide

To a solution of 8-amino-2-naphthol (15.00 g, 94.2 mmol) in 300 mL of isopropyl acetate and 250 mL of saturated $NaHCO_3$ solution at 0°C was added chloroacetyl chloride (18.75 mL, 235 mmol). 30 minutes, the layers were separated, and the organic layer was filtered through a glass frit to remove insolubles. Ethanolamine was added (20.9 mL, 377 mmol), and the reaction was warmed to 50°C for 2 hours, then cooled to room temperature. The solution was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The titled product was obtained as a dark brown solid which was used in the next reaction without further purification.

Step B: Preparation of N-(7-hydroxy-1-naphthyl)-2-[(2-(hydroxy)ethyl)*tert*-butoxycarbonyl amino]acetamide

To a solution of the product from Step A (7.50 g, 28.8 mmol) in 100 mL of tetrahydrofuran at 0°C was added di-*tert*-butyldicarbonate (6.29 g, 28.8 mmol). After 1.5 hours, the solution was concentrated *in vacuo to* provide the titled product as a dark brown foam which was used in the next reaction without further purification.

Step C: Preparation of 4-*tert*-butoxycarbonyl-1-(7-hydroxy-1-naphthyl)-2-piperazinone

To a solution of di-*tert*-butylazodicarboxylate (10.81 g, 43.2 mmol) in 60 mL of tetrahydrofuran at 0°C was added tributylphosphine (10.76 mL, 43.2 mmol) dropwise. After 10 minutes, a solution of the crude product from Step B (ca. 28.8 mmol) in 30 mL of tetrahydrofuran was added dropwise, and the reaction was allowed to warm to room temperature. After two hours, HPLC analysis showed partial conversion. The solution was cooled to 0°C, and additional portions of tributylphosphine (3.0 mL, 18 mmol) and di-*tert*-butylazodicarboxylate (4.6 g, 18 mmol) were added. The reaction was warmed to room temperature, and stirred for 16 hours. The solution was concentrated *in vacuo*, and the resulting product was purified by silica gel chromatography (0-5% $MeOH/CH_2Cl_2$) to provide the titled product as a dark brown foam, contaminated with tributylphosphine oxide impurity. This material was used in the next reaction without further purification.

Step D: Preparation of 1-(7-benzyloxy-1-naphthyl)-4-*tert*-butoxycarbonyl-2-piperazinone

To a solution of the product from Step C (ca. 28.8 mmol) in 150 mL of acetone was added potassium carbonate (20.0 g, 145 mmol), followed by benzyl bromide (3.45 mL, 29 mmol). The reaction was heated to reflux, and stirred for 18 hours. After cooling to room temperature, the solution was concentrated *in vacuo* to a 50 mL volume, poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product mixture was purified by silica gel chromatography (40-50% EtOAc/hexane) to provide the titled compound as a pale brown foam.

Step E: Preparation of 1-(7-benzyloxy-1-naphthyl)-2-piperazinone hydrochloride

Through a solution of the product from Step D (1.244 g, 2.88 mmol) in 50 mL of ethyl acetate at 0°C was bubbled anhydrous HCl gas for 5 minutes. After 30 minutes, the solution was concentrated *in vacuo*

to provide the titled salt as a brown powder (1.064 g) which was used in the next reaction without further purification.

Step F: Preparation of 1-(7-benzyloxy-1-naphthyl)-4-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-2-piperazinone

To a solution of the crude amine hydrochloride from Step E (2.88 mmol) in 15 mL of 1,2-dichloroethane was added 4Å powdered molecular sieves (2.0 g), followed by sodium triacetoxyborohydride (911 mg, 4.32 mmol). The aldehyde from Step G of Example 1 was added (659 mg, 2.88 mmol), and the reaction was stirred for 40 minutes. The reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The titled product was obtained as a brown foam which was used in the next reaction without further purification.

Step G: Preparation of 1-(7-hydroxy-1-naphthyl)-4-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-2-piperazinone trifluoroacetate

To a solution of the benzyl ether from Step F (1.563 g, 2.85 mmol) in 25 mL of 1:1 MeOH/EtOAc was added trifluoroacetic acid (1.0 mL) and 10% palladium on carbon (900 mg). The solution was stirred under a balloon atmosphere of hydrogen at room temperature. After 8 hours, the solution was filtered through celite, and the filter pad was rinsed with 1:1 MeOH/THF. Concentration *in vacuo* provided the titled product as a white foam which was used in the next reaction without further purification.

Step H: Preparation of Compound 6 dihydrochloride

To a solution of the product from Step G (ca. 2.85 mmol) in 50 mL of DMSO was added cesium carbonate (2.815 g, 8.64 mmol). The reaction was warmed to 55 °C under argon for 45 minutes, then cooled to room temperature. The solution was poured into EtOAc and washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chroma-

tography (5-8% $MeOH/CH_2Cl_2$) to provide the product as a pale yellow foam. A portion of this was taken up in CH_2Cl_2, treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product dihydrochloride as a pale yellow powder.

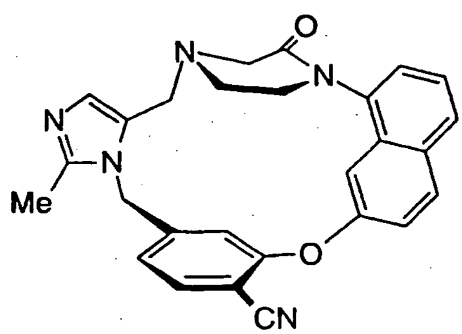
FAB mass spectrum m/e 436.3 (M+1).

Analysis calculated for $C_{26}H_{21}N_5O_2 \bullet 2.10\ HCl \bullet 1.10\ H_2O$:

	C, 58.77; H, 4.80; N, 13.18;
Found:	C, 58.82; H, 4.79; N, 12.67.

EXAMPLE 16

Preparation of (±)-19,20-Dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriazacyclo-octadecine-9-carbonitrile (8), dihydrochloride



8

Step A: Preparation of 4-cyano-3-fluorotoluene

To a degassed solution of 4-bromo-3-fluorotoluene (50.0 g, 264 mmol) in 500 mL of DMF was added $Zn(CN)_2$ (18.6 g, 159 mmol) and $Pd(PPh_3)_4$ (6.1 g, 5.3 mmol). The reaction was stirred at 80°C for 6 hours, then cooled to room temperature. The solution was poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography (0-5% EtOAc/hexane) provided the titled product.

Step B: Preparation of 4-cyano-3-fluorobenzylbromide

To a solution of the product from Step A (22.2 g, 165 mmol) in 220 mL of carbontetrachloride was added N-bromosuccinimide (29.2 g, 164 mmol) and benzoylperoxide (1.1g). The reaction was heated to reflux for 30 minutes, then cooled to room temperature. The solution was concentrated *in vacuo* to one-third the original volume, poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Analysis by 1H NMR indicated only partial conversion, so the crude material was resubjected to the same reaction conditions for 2.5 hours, using 18 g (102 mmol) of N-bromosuccinimide. After workup, the crude material was purified by silica gel chromatography (0-10% EtOAc/hexane) to provide the desired product.

Step C: Preparation of 1-(4-cyano-3-fluorobenzyl)-2-methyl-5-imidazolecarboxaldehyde

To a solution of the bromide from Step B (1.26 g, 5.9 mmol) in 10 mL of DMF at 0°C was added 4-formyl-2-methylimidazole (0.650 g, 5.9 mmol) and cesium carbonate (2.9 g, 8.9 mmol). After 2 hours, the reaction was poured into 2:1 EtOAc:hexane, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product mixture. The material was purified by silica gel chromatography (2-5% MeOH/$CHCl_3$) to provide the titled product along with the regioisomer 1-(4-cyano-3-fluorobenzyl)-2-methyl-4-imidazolecarboxaldehyde and a mixed fraction.

Step D: Preparation of 1-(7-benzyloxy-1-naphthyl)-4-[1-(4-cyano-3-fluorobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone

To a solution of the amine hydrochloride from Step E of example 15 (464 mg, 1.26 mmol) in 8 mL of 1,2-dichloroethane was added 4Å powdered molecular sieves (1.0 g), followed by sodium triacetoxyborohydride (401 mg, 1.89 mmol). The aldehyde from Step C was added (306 mg, 1.26 mmol), and the reaction was stirred for 16 hours. The reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried

(Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (2%MeOH/$CHCl_3$-5%MeOH/0.5% $NH_4OH/CHCl_3$) to provide the titled product.

Step E: Preparation of 1-(7-hydroxy-1-naphthyl)-4-[1-(4-cyano-3-fluorobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone

To a solution of the benzyl ether from Step D (419 mg, 0.75 mmol) in 6 mL of 1:1 MeOH/EtOAc was added 10% palladium on carbon (250 mg). The solution was stirred under a balloon atmosphere of hydrogen at room temperature. After 4 hours, another portion of Pd/C was added (250 mg). After 16 hours, the solution was filtered through celite. Concentration *in vacuo* provided the titled product which was used in the next reaction without further purification.

Step F: Preparation of Compound 8 dihydrochloride

To a solution of the product from Step F (304 mg, 0.67 mmol) in 13 mL of DMSO was added cesium carbonate (422 mg, 1.29 mmol). The reaction was warmed to 55 °C under argon for one hour, then cooled to room temperature. The solution was poured into EtOAc and washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was crystallized from $EtOH/Et_2O$ to yield 187 mg of pure material along with 29 mg of impure material. A portion of the pure material (10 mg) was taken up in CH_2Cl_2, treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product dihydrochloride as a white powder.

FAB mass spectrum m/e 450.3 (M+1).

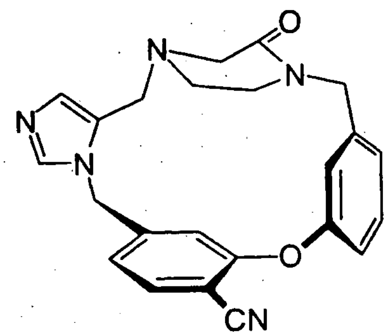
Analysis calculated for $C_{27}H_{23}N_5O_2 \bullet 2.00\ HCl \bullet 1.50\ H_2O$:

C, 59.02; H, 5.14; N, 12.75;

Found: C, 59.05; H, 5.26; N, 12.51.

EXAMPLE 16A

Preparation of 19,20-Dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile (Compound 3), dihydrochloride



3

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of

EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

<u>Step C:</u> <u>Preparation of 4-cyano-3-fluorotoluene</u>

To a degassed solution of 4-bromo-3-fluorotoluene (50.0 g, 264 mmol) in 500 mL of DMF was added $Zn(CN)_2$ (18.6 g, 159 mmol) and $Pd(PPh_3)_4$ (6.1 g, 5.3 mmol). The reaction was stirred at 80°C for 6 hours, then cooled to room temperature. The solution was poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography (0-5% EtOAc/hexane) provided the titled product.

<u>Step D:</u> <u>Preparation of 4-cyano-3-fluorobenzylbromide</u>

To a solution of the product from Step C (22.2 g, 165 mmol) in 220 mL of carbontetrachloride was added N-bromosuccinimide (29.2 g, 164 mmol) and benzoylperoxide (1.1g). The reaction was heated to reflux for 30 minutes, then cooled to room temperature. The solution was concentrated *in vacuo* to one-third the original volume, poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Analysis by 1H NMR indicated only partial conversion, so the crude material was resubjected to the same reaction conditions for 2.5 hours, using 18 g (102 mmol) of N-bromosuccinimide. After workup, the crude material was purified by silica gel chromatography (0-10% EtOAc/hexane) to provide the desired product.

<u>Step E:</u> <u>Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide</u>

A solution of the product from Step B (36.72 g, 96.14 mmol) and the product from Step D (20.67 g, 96.14 mmol) in 250 mL of EtOAc was stirred at 60°C for 20 hours, during which a white precipitate formed. The reaction was cooled to room temperature and filtered

to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume of 100 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 40 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 300 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step F: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(hydroxymethyl)imidazole

To a solution of the product from Step E (31.87 g, 89.77 mmol) in 300 mL of 2:1 THF/water at 0°C was added lithium hydroxide monohydrate (7.53 g, 179 mmol). After two hours, the reaction was concentrated *in vacuo* to a 100 mL volume, stored at 0°C for 30 minutes, then filtered and washed with 700 mL of cold water to provide a brown solid. This material was dried *in vacuo* next to P_2O_5 to provide the titled product as a pale brown powder which was sufficiently pure for use in the next step without further purification.

Step G: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-imidazolecarboxaldehyde

To a solution of the alcohol from Step F (2.31 g, 10.0 mmol) in 20 mL of DMSO at 0°C was added triethylamine (5.6 mL, 40 mmol), then SO_3-pyridine complex (3.89 g, 25 mmol). After 30 minutes, the reaction was poured into EtOAc, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde as a pale yellow powder which was sufficiently pure for use in the next step without further purification.

Step H: Preparation of 3-(benzyloxy)benzylmethanesulfonate

To a solution of 3-(benzyloxy)benzyl alcohol (1.546 g, 7.21 mmol) in 20 mL of CH_2Cl_2 at 0°C was added triethylamine (1.206 mL, 8.65 mmol) and methanesulfonic anhydride (1.257 g, 7.21 mmol). After 45 minutes, the solution was poured into EtOAc, washed with 10% HCl soln., sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product as a yellow oil.

<u>Step I</u>: Preparation of 1-[3-(benzyloxy)benzyl]-4-(benzyloxy)carbonyl-2-piperazinone

Sodium hydride (430 mg, 10.8 mmol as 60% dispersion in mineral oil) was triturated with hexanes, then suspended in 5 mL of DMF. After cooling to 0°C, 4-(benzyloxy)carbonyl-2-piperazinone was added (1.68 g, 7.18 mmol). After 15 minutes, a solution of the product from Step H (2.096 g, 7.18 mmol) in 2 mL of DMF was added, followed by a 1 mL DMF rinse. The reaction was warmed to room temperature, stirred for 30 minutes, then poured into EtOAc. The organic layer was washed with water, sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (60% EtAOAc/hexane) to produce the titled product as a pale yellow oil.

<u>Step J</u>: Preparation of 1-[3-(hydroxy)benzyl]-4-(*tert*-butyloxy)carbonyl-2-piperazinone

A solution of the product from Step I (806 mg, 1.87 mmol) and di-*tert*-butyl dicarbonate (408 mg, 1.87 mmol) and 10% palladium on carbon (330 mg) were stirred in a solution of 10 mL of THF under a balloon atmosphere of hydrogen. After 20 hours, the solution was filtered through celite, and the filter pad was rinsed with THF. Concentration *in vacuo* provided the titled product as a white foam.

<u>Step K</u>: Preparation of 1-[3-(hydroxy)benzyl]-2-piperazinone hydrochloride

Through a solution of the product from Step J (68 mg, 0.22 mmol) in 3.0 mL of ethyl acetate at 0°C was bubbled anhydrous HCl gas for 5 minutes. After 15 minutes, the solution was concentrated *in vacuo*

to provide the titled salt as a white foam which was used in the next reaction without further purification.

Step L: Preparation of 4-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-1-[3-(hydroxy)benzyl]-2-piperazinone

To a solution of the amine hydrochloride from Step K (theoretically 0.22 mmol) in 2 mL of 1,2-dichloroethane was added 4Å powdered molecular sieves (100 mg), followed by sodium triacetoxyborohydride (70 mg, 0.33 mmol). The aldehyde from Step G (51 mg, 0.22 mmol) was added, and the reaction was stirred for 16 hours. The reaction was poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The titled product was obtained as a pale yellow foam

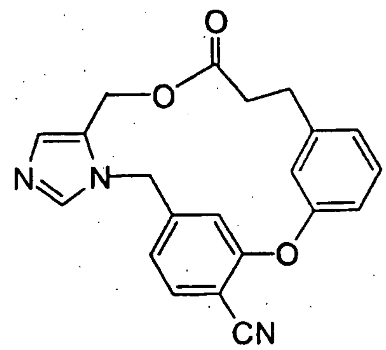
Step M: Preparation of Compound 3 dihydrochloride

To a solution of the product from Step L (60.6 mg, 0.15 mmol) in 1.5 mL of DMSO was added cesium carbonate (148 mg, 0.45 mmol). The reaction was warmed to 55°C under argon for 20 minutes, then cooled to room temperature. The solution was poured into EtOAc and washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (5-6% $MeOH/CH_2Cl_2$), taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product dihydrochloride as a white powder.
FAB mass spectrum m/e 400.0 (M+1).

Analysis calculated for $C_{23}H_{21}N_5O_2 \bullet 2.70\ HCl \bullet 1.00\ H_2O$:
C, 53.55; H, 5.02; N, 13.57;
Found: C, 53.64; H, 5.04; N, 13.05.

EXAMPLE 17

Preparation of 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclononadecine-9-carbonitrile (9), hydrochloride salt



9

Step A: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step B: Preparation of 1-triphenylmethyl-4-(acetoxymethyl) imidazole

Alcohol from Step A (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

Step C: Preparation of 4-cyano-3-fluorotoluene

To a degassed solution of 4-bromo-3-fluorotoluene (50.0 g, 264 mmol) in 500 mL of DMF was added $Zn(CN)_2$ (18.6 g, 159 mmol) and $Pd(PPh_3)_4$ (6.1 g, 5.3 mmol). The reaction was stirred at 80°C for 6 hours, then cooled to room temperature. The solution was poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Purification by silica gel chromatography (0-5% EtOAc/hexane) provided the titled product.

Step D: Preparation of 4-cyano-3-fluorobenzylbromide

To a solution of the product from Step C (22.2 g, 165 mmol) in 220 mL of carbontetrachloride was added N-bromosuccinimide (29.2 g, 164 mmol) and benzoylperoxide (1.1g). The reaction was heated to reflux for 30 minutes, then cooled to room temperature. The solution was concentrated *in vacuo* to one-third the original volume, poured into EtOAc, washed with water, sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. Analysis by ^1H NMR indicated only partial conversion, so the crude material was resubjected to the same reaction conditions for 2.5 hours, using 18 g (102 mmol) of N-bromosuccinimide. After workup, the crude material was purified by silica gel chromatography (0-10% EtOAc/hexane) to provide the desired product.

Step E: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step B (36.72 g, 96.14 mmol) and the product from Step D (20.67 g, 96.14 mmol) in 250 mL of EtOAc was stirred at 60°C for 20 hours, during which a white precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60°C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 40 mL, reheated at 60°C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined,

dissolved in 300 mL of methanol, and warmed to 60°C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step F: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-(hydroxymethyl) imidazole

To a solution of the product from Step E (31.87 g, 89.77 mmol) in 300 mL of 2:1 THF/water at 0°C was added lithium hydroxide monohydrate (7.53 g, 179 mmol). After two hours, the reaction was concentrated *in vacuo* to a 100 mL volume, stored at 0°C for 30 minutes, then filtered and washed with 700 mL of cold water to provide a brown solid. This material was dried *in vacuo* next to P_2O_5 to provide the titled product as a pale brown powder which was sufficiently pure for use in the next step without further purification.

Step G: Preparation of 1-(4-cyano-3-fluorobenzyl)-5-[((3-(3-hydroxyphenyl)propionyl)oxy)methyl]imidazole

To a solution of the alcohol from Step F (79.7 mg, 0.345 mmol) and triphenylphosphine (90.0 mg, 0.345 mmol) in 0.5 mL of THF was added a solution of diethylazodicarboxylate (0.054 mL, 0.345 mmol) and 3-(3-hydroxyphenyl)propionic acid (57 mg, 0.34 mmol)in 0.5 mL of THF. After 10 minutes, HPLC analysis indicated 60% conversion. Additional triphenylphosphine (45 mg, 0.17 mmol) and diethylazodicarboxylate (0.027 mL, 0.17 mmol) were added, and the reaction was stirred for 10 more minutes. The solution was concentrated *in vacuo*, then purified by silica gel chromatography (3% MeOH/CH_2Cl_2) to provide the desired product as a white foam.

Step H: Preparation of Compound 9, hydrochloride salt

To a solution of the phenol from Step G (54 mg, 0.14 mmol) in 1.0 mL of DMSO was added cesium carbonate (92 mg, 0.28 mmol). The reaction was warmed to 55°C for 20 minutes, then cooled to room temperature. The solution was poured into EtOAc, washed with sat. aq.

$NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was purified by silica gel chromatography (3-4% $MeOH/CH_2Cl_2$), taken up in CH_2Cl_2 and treated with excess 1 M HCl/ether solution, and concentrated *in vacuo* to provide the titled product hydrochloride as a white powder.
FAB mass spectrum m/e 360.1 (M+1).

Analysis calculated for $C_{21}H_{17}N_3O_3 \bullet 1.00\ HCl \bullet 1.00\ H_2O$:
C, 60.95; H, 4.87; N, 10.15;
Found: C, 60.84; H, 4.88; N, 10.12.

EXAMPLE 18

In vitro inhibition of ras farnesyl transferase

Transferase Assays. Isoprenyl-protein transferase activity assays are carried out at 30°C unless noted otherwise. A typical reaction contains (in a final volume of 50 μL): [^{3}H]farnesyl diphosphate, Ras protein , 50 mM HEPES, pH 7.5, 5 mM $MgCl_2$, 5 mM dithiothreitol, 10 μM $ZnCl_2$, 0.1% polyethyleneglycol (PEG) (15,000-20,000 mw) and isoprenyl-protein transferase. The FPTase employed in the assay is prepared by recombinant expression as described in Omer, C.A., Kral, A.M., Diehl, R.E., Prendergast, G.C., Powers, S., Allen, C.M., Gibbs, J.B. and Kohl, N.E. (1993) *Biochemistry* 32:5167-5176. After thermally pre-equilibrating the assay mixture in the absence of enzyme, reactions are initiated by the addition of isoprenyl-protein transferase and stopped at timed intervals (typically 15 min) by the addition of 1 M HCl in ethanol (1 mL). The quenched reactions are allowed to stand for 15 m (to complete the precipitation process). After adding 2 mL of 100% ethanol, the reactions are vacuum-filtered through Whatman GF/C filters. Filters are washed four times with 2 mL aliquots of 100% ethanol, mixed with scintillation fluid (10 mL) and then counted in a Beckman LS3801 scintillation counter.

For inhibition studies, assays are run as described above, except test compounds or compositions are prepared as concentrated

solutions in 100% dimethyl sulfoxide and then diluted 20-fold into the enzyme assay mixture. Substrate concentrations for inhibitor IC_{50} determinations are as follows: FTase, 650 nM Ras-CVLS (SEQ.ID.NO.: 1), 100 nM farnesyl diphosphate.

The compounds of the instant invention described in the above Examples 1-17 were tested for inhibitory activity against human FPTase by the assay described above and were found to have an IC_{50} of ≤ 1 μM.

EXAMPLE 19

Modified*In vitro* GGTase inhibition assay

The modified geranylgeranyl-protein transferase inhibition assay is carried out at room temperature. A typical reaction contains (in a final volume of 50 μL): [^{3}H]geranylgeranyl diphosphate, biotinylated Ras peptide, 50 mM HEPES, pH 7.5, a modulating anion (for example 10 mM glycerophosphate or 5mM ATP), 5 mM $MgCl_2$, 10 μM $ZnCl_2$, 0.1% PEG (15,000-20,000 mw), 2 mM dithiothreitol, and geranylgeranyl-protein transferase type I(GGTase). The GGTase-type I enzyme employed in the assay is prepared as described in U.S. Pat. No. 5,470,832, incorporated by reference. The Ras peptide is derived from the K4B-Ras protein and has the following sequence: biotinyl-GKKKKKKSKTKCVIM (single amino acid code) (SEQ.ID.NO.: 2). Reactions are initiated by the addition of GGTase and stopped at timed intervals (typically 15 min) by the addition of 200 μL of a 3 mg/mL suspension of streptavidin SPA beads (Scintillation Proximity Assay beads, Amersham) in 0.2 M sodium phosphate, pH 4, containing 50 mM EDTA, and 0.5% BSA. The quenched reactions are allowed to stand for 2 hours before analysis on a Packard TopCount scintillation counter.

For inhibition studies, assays are run as described above, except test compounds or compositions are prepared as concentrated solutions in 100% dimethyl sulfoxide and then diluted 25-fold into the enzyme assay mixture. IC_{50} values are determined with Ras peptide near K_M concentrations. Enzyme and substrate concentrations for

inhibitor IC_{50} determinations are as follows: 75 pM GGTase-I, 1.6 μM Ras peptide, 100 nM geranylgeranyl diphosphate.

EXAMPLE 20

Cell-based*in vitro* ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound or composition (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labeled in 3 ml methionine-free DMEM supple-mented with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[35S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 21

Cell-based*in vitro* growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the instant compositions and the compounds useful in the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the test compound or composition (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

EXAMPLE 22

Construction of SEAP reporter plasmid pDSE100

The SEAP reporter plasmid, pDSE100 was constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is derived from the plasmid pSEAP2-Basic (Clontech, Palo Alto, CA). The plasmid pCMV-RE-AKI contains 5 sequential copies of the 'dyad symmetry response element' cloned upstream of a 'CAT-TATA' sequence derived from the cytomegalovirus immediate early promoter. The plasmid also contains a bovine growth hormone poly-A sequence.

The plasmid, pDSE100 was constructed as follows. A restriction fragment encoding the SEAP coding sequence was cut out

of the plasmid pSEAP2-Basic using the restriction enzymes EcoR1 and HpaI. The ends of the linear DNA fragments were filled in with the Klenow fragment of E. coli DNA Polymerase I. The 'blunt ended' DNA containing the SEAP gene was isolated by electrophoresing the digest in an agarose gel and cutting out the 1694 base pair fragment. The vector plasmid pCMV-RE-AKI was linearized with the restriction enzyme Bgl-II and the ends filled in with Klenow DNA Polymerase I. The SEAP DNA fragment was blunt end ligated into the pCMV-RE-AKI vector and the ligation products were transformed into DH5-alpha E. coli cells (Gibco-BRL). Transformants were screened for the proper insert and then mapped for restriction fragment orientation. Properly oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid contains the SEAP coding sequence downstream of the DSE and CAT-TATA promoter elements and upstream of the BGH poly-A sequence.

Alternative Construction of SEAP reporter plasmid, pDSE101

The SEAP repotrer plasmid, pDSE101 is also constructed by ligating a restriction fragment containing the SEAP coding sequence into the plasmid pCMV-RE-AKI. The SEAP gene is derived from plasmid pGEM7zf(-)/SEAP.

The plasmid pDSE101 was constructed as follows: A restriction fragment containing part of the SEAP gene coding sequence was cut out of the plasmid pGEM7zf(-)/SEAP using the restriction enzymes Apa I and KpnI. The ends of the linear DNA fragments were chewed back with the Klenow fragment of E. coli DNA Polymerase I. The "blunt ended" DNA containing the truncated SEAP gene was isolated by electrophoresing the digest in an agarose gel and cutting out the 1910 base pair fragment. This 1910 base pair fragment was ligated into the plasmid pCMV-RE-AKI which had been cut with Bgl-II and filled in with E. coli Klenow fragment DNA polymerase. Recombinant plasmids were screened for insert orientation and sequenced through the ligated junctions. The plasmid pCMV-RE-AKI is derived from plasmid pCMVIE-AKI-DHFR (Whang , Y., Silberklang, M., Morgan,

A., Munshi, S., Lenny, A.B., Ellis, R.W., and Kieff, E. (1987) J. Virol., 61, 1796-1807) by removing an EcoRI fragment containing the DHFR and Neomycin markers. Five copies of the fos promoter serum response element were inserted as described previously (Jones, R.E., Defeo-Jones, D., McAvoy, E.M., Vuocolo, G.A., Wegrzyn, R.J., Haskell, K.M. and Oliff, A. (1991) Oncogene, 6, 745-751) to create plasmid pCMV-RE-AKI.

The plasmid pGEM7zf(-)/SEAP was constructed as follows. The SEAP gene was PCRed, in two segments from a human placenta cDNA library (Clontech) using the following oligos.

Sense strand N-terminal SEAP : 5'
GAGAGGGAATTCGGGCCCTTCCTGCAT
GCTGCTGCTGCTGCTGCTGCTGGGC 3' (SEQ.ID.NO.:3)

Antisense strand N-terminal SEAP: 5'
GAGAGAGCTCGAGGTTAACCCGGGT
GCGCGGCGTCGGTGGT 3' (SEQ.ID.NO.:4)

Sense strand C-terminal SEAP: 5'
GAGAGAGTCTAGAGTTAACCCGTGGTCC
CCGCGTTGCTTCCT 3' (SEQ.ID.NO.:5)

Antisense strand C-terminal SEAP: 5'
GAAGAGGAAGCTTGGTACCGCCACTG
GGCTGTAGGTGGTGGCT 3' (SEQ.ID.NO.:6)

The N-terminal oligos (SEQ.ID.NO.: 4 and SEQ.ID.NO.: 5) were used to generate a 1560 bp N-terminal PCR product that contained EcoRI and HpaI restriction sites at the ends. The Antisense N-terminal oligo (SEQ.ID.NO.: 4) introduces an internal translation STOP codon within the SEAP gene along with the HpaI site. The C-terminal oligos (SEQ.ID.NO.: 5 and SEQ.ID.NO.: 6) were used to amplify a 412 bp C-terminal PCR product containing HpaI and HindIII restriction sites. The sense strand C-terminal oligo (SEQ.ID.NO.: 5) introduces

the internal STOP codon as well as the HpaI site. Next, the N-terminal amplicon was digested with EcoRI and HpaI while the C-terminal amplicon was digested with HpaI and HindIII. The two fragments comprising each end of the SEAP gene were isolated by electrophoresing the digest in an agarose gel and isolating the 1560 and 412 base pair fragments. These two fragments were then co-ligated into the vector pGEM7zf(-) (Promega) which had been restriction digested with EcoRI and HindIII and isolated on an agarose gel. The resulting clone, pGEM7zf(-)/SEAP contains the coding sequence for the SEAP gene from amino acids.

Construction of a constitutively expressing SEAP plasmid pCMV-SEAP

An expression plasmid constitutively expressing the SEAP protein was created by placing the sequence encoding a truncated SEAP gene downstream of the cytomegalovirus (CMV) IE-1 promoter. The expression plasmid also includes the CMV intron A region 5' to the SEAP gene as well as the 3' untranslated region of the bovine growth hormone gene 3' to the SEAP gene.

The plasmid pCMVIE-AKI-DHFR (Whang et al, 1987) containing the CMV immediate early promoter was cut with EcoRI generating two fragments. The vector fragment was isolated by agarose electrophoresis and religated. The resulting plasmid is named pCMV-AKI. Next, the cytomegalovirus intron A nucleotide sequence was inserted downstream of the CMV IE1 promter in pCMV-AKI. The intron A sequence was isolated from a genomic clone bank and sub-cloned into pBR322 to generate plasmid p16T-286. The intron A sequence was mutated at nucleotide 1856 (nucleotide numbering as in Chapman, B.S., Thayer, R.M., Vincent, K.A. and Haigwood, N.L., Nuc.Acids Res. 19, 3979-3986) to remove a SacI restriction site using site directed mutagenesis. The mutated intron A sequence was PCRed from the plasmid p16T-287 using the following oligos.

Sense strand: 5' GGCAGAGCTCGTTTAGTGAACCGTCAG 3' (SEQ.ID.NO.: 7)

Antisense strand: 5' GAGAGATCTCAAGGACGGTGACTGCAG 3' (SEQ.ID.NO.: 8)

These two oligos generate a 991 base pair fragment with a SacI site incorporated by the sense oligo and a Bgl-II fragment incorporated by the antisense oligo. The PCR fragment is trimmed with SacI and Bgl-II and isolated on an agarose gel. The vector pCMV-AKI is cut with SacI and Bgl-II and the larger vector fragment isolated by agarose gel electrophoresis. The two gel isolated fragments are ligated at their respective SacI and Bgl-II sites to create plasmid pCMV-AKI-InA.

The DNA sequence encoding the truncated SEAP gene is inserted into the pCMV-AKI-InA plasmid at the Bgl-II site of the vector. The SEAP gene is cut out of plasmid pGEM7zf(-)/SEAP (described above) using EcoRI and HindIII. The fragment is filled in with Klenow DNA polymerase and the 1970 base pair fragment isolated from the vector fragment by agarose gel electrophoresis. The pCMV-AKI-InA vector is prepared by digesting with Bgl-II and filling in the ends with Klenow DNA polymerase. The final construct is generated by blunt end ligating the SEAP fragment into the pCMV-AKI-InA vector. Transformants were screened for the proper insert and then mapped for restriction fragment orientation. Properly oriented recombinant constructs were sequenced across the cloning junctions to verify the correct sequence. The resulting plasmid, named pCMV-SEAP, contains a modified SEAP sequence downstream of the cytomegalovirus immediately early promoter IE-1 and intron A sequence and upstream of the bovine growth hormone poly-A sequence. The plasmid expresses SEAP in a constitutive manner when transfected into mammalian cells.

Cloning of a Myristylated viral-H-*ras* expression plasmid

A DNA fragment containing viral-H-*ras* can be PCRed from plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) or "HB-11 (deposited in the ATCC under Budapest Treaty on August 27, 1997, and designated ATCC 209,218) using the following oligos.

Sense strand:
5'TCTCCTCGAGGCCACCATGGGGAGTAGCAAGAGCAAGCCTAA GGACCCCAGCCAGCGCCGGATGACAGAATACAAGCTTGTGGTG G 3'. (SEQ.ID.NO.: 9)

Antisense:
5'CACATCTAGATCAGGACAGCACAGACTTGCAGC 3'. (SEQ.ID.NO.: 10)

A sequence encoding the first 15 aminoacids of the v-src gene, containing a myristylation site, is incorporated into the sense strand oligo. The sense strand oligo also optimizes the 'Kozak' translation initiation sequence immediately 5' to the ATG start site. To prevent prenylation at the viral-*ras* C-terminus, cysteine 186 would be mutated to a serine by substituting a G residue for a C residue in the C-terminal antisense oligo. The PCR primer oligos introduce an XhoI site at the 5' end and a XbaI site at the 3'end. The XhoI-XbaI fragment can be ligated into the mammalian expression plasmid pCI (Promega) cut with XhoI and XbaI. This results in a plasmid in which the recombinant myr-viral-H-ras gene is constitutively transcribed from the CMV promoter of the pCI vector.

Cloning of a viral-H-*ras*-CVLL expression plasmid

A viral-H-*ras* clone with a C-terminal sequence encoding the amino acids CVLL can be cloned from the plasmid "H-1" (Ellis R. et al. J. Virol. **36**, 408, 1980) or "HB-11 (deposited in the ATCC under Budapest Treaty on August 27, 1997, and designated ATCC 209,218) by PCR using the following oligos.

Sense strand:
5'TCTCCTCGAGGCCACCATGACAGAATACAAGCTTGTGGTGG-3' (SEQ.ID.NO.: 11)

Antisense strand:
5'CACTCTAGACTGGTGTCAGAGCAGCACACACTTGCAGC-3' (SEQ.ID.NO.: 12)

The sense strand oligo optimizes the 'Kozak' sequence and adds an XhoI site. The antisense strand mutates serine 189 to leucine and adds an XbaI site. The PCR fragment can be trimmed with XhoI and XbaI and ligated into the XhoI-XbaI cut vector pCI (Promega). This results in a plasmid in which the mutated viral-H-*ras*-CVLL gene is constitutively transcribed from the CMV promoter of the pCI vector.

<u>Cloning of c-H-*ras*-Leu61 expression plasmid</u>

The human c-H-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

<u>Sense strand:</u>
5'-GAGAGAATTCGCCACCATGACGGAATATAAGCTGGTGG-3'
(SEQ.ID.NO.: 13)

<u>Antisense strand:</u>
5'-GAGAGTCGACGCGTCAGGAGAGCACACACTTGC-3'
(SEQ.ID.NO.: 14)

The primers will amplify a c-H-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-H-ras fragment can be ligated ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glutamine-61 to a leucine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-CCGCCGGCCTGGAGGAGTACAG-3' (SEQ.ID.NO.: 15)

After selection and sequencing for the correct nucleotide substitution, the mutated c-H-*ras*-Leu61 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-H-*ras*-Leu61 from the CMV promoter of the pCI vector.

Cloning of a c-N-*ras*-Val-12 expression plasmid

The human c-N-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGAATTCGCCACCATGACTGAGTACAAACTGGTGG-3' (SEQ.ID.NO.: 16)

Antisense strand:
5'-GAGAGTCGACTTGTTACATCACCACACATGGC-3' (SEQ.ID.NO.: 17)

The primers will amplify a c-N-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, an EcoRI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with EcoRI and Sal I, the c-N-ras fragment can be ligated into an EcoRI -Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of glycine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTTGGAGCAGTTGGTGTTGGG-3' (SEQ.ID.NO.: 18)

After selection and sequencing for the correct nucleotide substitution, the mutated c-N-*ras*-Val-12 can be excised from the pAlter-1 vector, using EcoRI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with EcoRI and Sal I. The new recombinant plasmid will constitutively transcribe c-N-*ras*-Val-12 from the CMV promoter of the pCI vector.

Cloning of a c-K-*ras*-Val-12 expression plasmid

The human c-K-*ras* gene can be PCRed from a human cerebral cortex cDNA library (Clontech) using the following oligonucleotide primers.

Sense strand:
5'-GAGAGGTACCGCCACCATGACTGAATATAAACTTGTGG-3' (SEQ.ID.NO.: 19)

Antisense strand:
5'-CTCTGTCGACGTATTTACATAATTACACACTTTGTC-3'
(SEQ.ID.NO.: 20)

The primers will amplify a c-K-*ras* encoding DNA fragment with the primers contributing an optimized 'Kozak' translation start sequence, a KpnI site at the N-terminus and a Sal I stite at the C-terminal end. After trimming the ends of the PCR product with Kpn I and Sal I, the c-K-*ras* fragment can be ligated into a KpnI - Sal I cut mutagenesis vector pAlter-1 (Promega). Mutation of cysteine-12 to a valine can be accomplished using the manufacturer's protocols and the following oligonucleotide:

5'-GTAGTTGGAGCTGTTGGCGTAGGC-3' (SEQ.ID.NO.: 21)

After selection and sequencing for the correct nucleotide substitution, the mutated c-K-*ras*-Val-12 can be excised from the pAlter-1 vector, using KpnI and Sal I, and be directly ligated into the vector pCI (Promega) which has been digested with KpnI and Sal I. The new recombinant plasmid will constitutively transcribe c-K-*ras*-Val-12 from the CMV promoter of the pCI vector.

SEAP assay

Human C33A cells (human epitheial carcenoma - ATTC collection) are seeded in 10cm tissue culture plates in DMEM + 10% fetal calf serum + 1X Pen/Strep + 1X glutamine + 1X NEAA. Cells are grown at 37°C in a 5% CO_2 atmosphere until they reach 50 -80% of confluency.

The transient transfection is performed by the $CaPO_4$ method (Sambrook et al., 1989). Thus, expression plasmids for H-*ras*, N-*ras*, K-*ras*, Myr-*ras* or H-*ras*-CVLL are co-precipitated with the DSE-SEAP reporter construct. For 10cm plates 600μl of $CaCl_2$ -DNA solution is added dropwise while vortexing to 600μl of 2X HBS buffer to give 1.2ml of precipitate solution (see recipes below). This is allowed to sit at room temperature for 20 to 30 minutes. While the precipitate is forming, the media on the C33A cells is replaced with DMEM (minus phenol red; Gibco cat. # 31053-028)+ 0.5% charcoal stripped calf serum + 1X (Pen/

Strep, Glutamine and nonessential aminoacids). The $CaPO_4$-DNA precipitate is added dropwise to the cells and the plate rocked gently to distribute. DNA uptake is allowed to proceed for 5-6 hrs at 37°C under a 5% CO_2 atmosphere.

Following the DNA incubation period, the cells are washed with PBS and trypsinized with 1ml of 0.05% trypsin. The 1 ml of trypsinized cells is diluted into 10ml of phenol red free DMEM + 0.2% charcoal stripped calf serum + 1X (Pen/Strep, Glutamine and NEAA). Transfected cells are plated in a 96 well microtiter plate (100µl/well) to which drug, diluted in media, has already been added in a volume of 100µl. The final volume per well is 200µl with each drug concentration repeated in triplicate over a range of half-log steps.

Incubation of cells and test compounds or compositions is for 36 hrs at 37°Cunder CO_2. At the end of the incubation period, cells are examined microscopically for evidence of cell distress. Next, 100µl of media containing the secreted alkaline phosphatase is removed from each well and transferred to a microtube array for heat treatment at 65°C for 1 hr to inactivate endogenous alkaline phosphatases (but not the heat stable secreted phosphatase).

The heat treated media is assayed for alkaline phosphatase by a luminescence assay using the luminescence reagent CSPD® (Tropix, Bedford, Mass.). A volume of 50 µl media is combined with 200 µl of CSPD cocktail and incubated for 60 minutes at room temperature. Luminesence is monitored using an ML2200 microplate luminometer (Dynatech). Luminescence reflects the level of activation of the fos reporter construct stimulated by the transiently expressed protein.

<u>DNA-$CaPO_4$ precipitate for 10cm. plate of cells</u>

Ras expression plasmid (1µg/µl)	10µl
DSE-SEAP Plasmid (1µg/µl)	2µl
Sheared Calf Thymus DNA (1µg/µl)	8µl
2M $CaCl_2$	74µl
dH_2O	506µl

2X HBS Buffer

280mM NaCl

10mM KCl

1.5mM Na_2HPO_4 $2H_2O$

12mM dextrose

50mM HEPES

Final pH = 7.05

Luminesence Buffer (26ml)

Assay Buffer	20ml
Emerald Reagent™ (Tropix)	2.5ml
100mM homoarginine	2.5ml
CSPD Reagent® (Tropix)	1.0ml

Assay Buffer

Add 0.05M Na_2CO_3 to 0.05M $NaHCO_3$ to obtain pH 9.5.

Make 1mM in $MgCl_2$

EXAMPLE 23

The processing assays employed in this example and in Example 24 are modifications of that described by DeClue et al [Cancer Research 51, 712-717, 1991].

K4B-Ras processing inhibition assay

PSN-1 (human pancreatic carcinoma) are used for analysis of protein processing. Subconfluent cells in 100 mm dishes are fed with 3.5 ml of media (methionine-free RPMI supplemented with 2% fetal bovine serum or cysteine-free/methionine-free DMEM supplemented with 0.035 ml of 200 mM glutamine (Gibco), 2% fetal bovine serum, respectively) containing the desired concentration of farnesyl-protein transferase inhibitor, HMG-CoA reductase inhibitor, instant combination composition or solvent alone. Test compounds or compositions are prepared as 1000x concentrated solutions in DMSO to yield a final solvent concentration of 0.1%. Following incubation at 37°C

for two hours 204 μCi/ml [^{35}S]Pro-Mix (Amersham, cell labeling grade) is added.

After introducing the label amino acid mixture, the cells are incubated at 37^{o}C for an additional period of time (typically 6 to 24 hours). The media is then removed and the cells are washed once with cold PBS. The cells are scraped into 1 ml of cold PBS, collected by centrifugation (10,000 x g for 10 sec at room temperature), and lysed by vortexing in 1 ml of lysis buffer (1% Nonidet P-40, 20 mM HEPES, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.5% deoxycholate, 0.1% SDS, 1 mM DTT, 10 μg/ml AEBSF, 10 μg/ml aprotinin, 2 μg/ml leupeptin and 2 μg/ml antipain). The lysate is then centrifuged at 15,000 x g for 10 min at 4^{o}C and the supernatant saved.

For immunoprecipitation of Ki4B-Ras, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 8 μg of the pan Ras monoclonal antibody, Y13-259, added. The protein/antibody mixture is incubated on ice at 4^{o}C for 24 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4^{o}C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 μl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer 0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The second protein/antibody mixture is incubated on ice at 4^{o}C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) coated with rabbit antiserum to rat IgG (Cappel) by tumbling at 4^{o}C

for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Ras is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Ras visualized by fluorography.

hDJ processing inhibition assay

PSN-1 cells are seeded in 24-well assay plates. For each compoundor composition to be tested, the cells are treated with a minimum of seven concentrations in half-log steps. The final solvent (DMSO) concentration is 0.1%. A vehicle-only control is included on each assay plate. The cells are treated for 24 hours at 37°C / 5% CO_2.

The growth media is then aspirated and the samples are washed with PBS. The cells are lysed with SDS-PAGE sample buffer containing 5% 2-mercaptoethanol and heated to 95°C for 5 minutes. After cooling on ice for 10 minutes, a mixture of nucleases is added to reduce viscosity of the samples.

The plates are incubated on ice for another 10 minutes. The samples are loaded onto pre-cast 8% acrylamide gels and electrophoresed at 15 mA/gel for 3-4 hours. The samples are then transferred from the gels to PVDF membranes by Western blotting.

The membranes are blocked for at least 1 hour in buffer containing 2% nonfat dry milk. The membranes are then treated with a monoclonal antibody to HDJ-2 (Neomarkers Cat. # MS-225), washed, and treated with an alkaline phosphatase-conjugated secondary antibody. The membranes are then treated with a fluorescent detection reagent and scanned on a phosphorimager.

For each sample, the percent of total signal corresponding to the unprenylated species of HDJ (the slower-migrating species) is calculated by densitometry. Dose-response curves and IC50 values are generated using 4-parameter curve fits in SigmaPlot software.

EXAMPLE 24

K4B-Ras processing inhibition assay

PSN-1 (human pancreatic carcinoma) cells are used for analysis of protein processing. Subconfluent cells in 150 mm dishes are fed with 20 ml of media (RPMI supplemented with 15% fetal bovine serum) containing the desired concentration of test composition, compound, lovastatin or solvent alone. Cells treated with lovastatin (5-10 μM), a compound that blocks Ras processing in cells by inhibiting a rate-limiting step in the isoprenoid biosynthetic pathway, serve as a positive control. Test compounds and compositions are prepared as 1000x concentrated solutions in DMSO to yield a final solvent concentration of 0.1%.

The cells are incubated at 37°C for 24 hours, the media is then removed and the cells are washed twice with cold PBS. The cells are scraped into 2 ml of cold PBS, collected by centrifugation (10,000 x g for 5 min at 4°C) and frozen at -70 °C. Cells are lysed by thawing and addition of lysis buffer (50 mM HEPES, pH 7.2, 50 mM NaCl, 1% CHAPS, 0.7 μg/ml aprotinin, 0.7 μg/ml leupeptin 300 μg/ml pefabloc, and 0.3 mM EDTA). The lysate is then centrifuged at 100,000 x g for 60 min at 4°C and the supernatant saved. The supernatant may be subjected to SDS-PAGE, HPLC analysis, and/or chemical cleavage techniques.

The lysate is applied to a HiTrap-SP (Pharmacia Biotech) column in buffer A (50 mM HEPES pH 7.2) and resolved by gradient in buffer A plus 1 M NaCl. Peak fractions containing Ki4B-Ras are pooled, diluted with an equal volume of water and immunoprecipitated with the pan Ras monoclonal antibody, Y13-259 linked to agarose or Kirsten-ras specific monoclonal antibody, c-K-ras Ab-1 (Calbiochem). The protein/antibody mixture is incubated at 4°C for 12 hours. The immune complex is washed 3 times with PBS , followed by 3 times with water. The Ras is eluted from the beads by either high pH conditions (pH>10) or by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant may be subjected to SDS-PAGE, HPLC analysis, and/or chemical cleavage techniques.

EXAMPLE 25

Rap1 processing inhibition assay

Protocol A:

Cells are labeled, incubated and lysed as described in Example 23.

For immunoprecipitation of Rap1, samples of lysate supernatant containing equal amounts of protein are utilized. Protein concentration is determined by the bradford method utilizing bovine serum albumin as a standard. The appropriate volume of lysate is brought to 1 ml with lysis buffer lacking DTT and 2 μg of the Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech), is added. The protein/ antibody mixture is incubated on ice at 4°C for 1 hour. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in 100 μl elution buffer (10 mM Tris pH 7.4, 1% SDS). The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation (15,000 x g for 30 sec. at room temperature).

The supernatant is added to 1 ml of Dilution Buffer (0.1% Triton X-100, 5 mM EDTA, 50 mM NaCl, 10 mM Tris pH 7.4) with 2 μg Rap1 antibody, Rap1/Krev1 (121) (Santa Cruz Biotech). The second protein/antibody mixture is incubated on ice at 4°C for 1-2 hours. The immune complex is collected on pansorbin (Calbiochem) by tumbling at 4°C for 45 minutes. The pellet is washed 3 times with 1 ml of lysis buffer lacking DTT and protease inhibitors and resuspended in Laemmli sample buffer. The Rap1 is eluted from the beads by heating at 95°C for 5 minutes, after which the beads are pelleted by brief centrifugation. The supernatant is subjected to SDS-PAGE on a 12% acrylamide gel (bis-acrylamide:acrylamide, 1:100), and the Rap1 visualized by fluorography.

Protocol B:

PSN-1 cells are passaged every 3-4 days in 10cm plates, splitting near-confluent plates 1:20 and 1:40. The day before the assay is set up, 5×10^6 cells are plated on 15cm plates to ensure the same stage

of confluency in each assay. The media for these cells is RPM1 1640 (Gibco), with 15% fetal bovine serum and 1x Pen/Strep antibiotic mix.

The day of the assay, cells are collected from the 15cm plates by trypsinization and diluted to 400,000 cells/ml in media. 0.5ml of these diluted cells are added to each well of 24-well plates, for a final cell number of 200,000 per well. The cells are then grown at 37°C overnight.

The compounds or compositionsto be assayed are diluted in DMSO in 1/2-log dilutions. The range of final concentrations to be assayed is generally 0.1-100μM. Four concentrations per compound is typical. The compounds are diluted so that each concentration is 1000x of the final concentration (i.e., for a 10μM data point, a 10mM stock of the compound is needed).

2μL of each 1000x compound stock is diluted into 1ml media to produce a 2X stock of compound. A vehicle control solution (2μL DMSO to 1ml media), is utilized. 0.5 ml of the 2X stocks of compound are added to the cells.

After 24 hours, the media is aspirated from the assayplates. Each well is rinsed with 1ml PBS, and the PBS is aspirated. 180μL SDS-PAGE sample buffer (Novex) containing 5% 2-mercaptoethanol is added to each well. The plates are heated to 100°C for 5 minutes using a heat block containing an adapter for assay plates. The plates are placed on ice. After 10 minutes, 20μL of an RNAse/DNase mix is added per well. This mix is 1mg/ml DNaseI (Worthington Enzymes), 0.25mg/ml Rnase A (Worthington Enzymes), 0.5M Tris-HCl pH8.0 and 50mM $MgCl_2$. The plate is left on ice for 10 minutes. Samples are then either loaded on the gel, or stored at -70°C until use.

Each assay plate (usually 3 compounds, each in 4-point titrations, plus controls) requires one 15-well 14% Novex gel. 25μl of each sample is loaded onto the gel. The gel is run at 15mA for about 3.5 hours. It is important to run the gel far enough so that there will be adequate separation between 21kd (Rap1) and 29kd (Rab6).

The gels are then transferred to Novex pre-cut PVDF membranes for 1.5 hours at 30V (constant voltage). Immediately after transferring, the membranes are blocked overnight in 20ml Western

blocking buffer (2% nonfat dry milk in Western wash buffer (PBS + 0.1% Tween-20). If blocked over the weekend, 0.02% sodium azide is added. The membranes are blocked at 4°C with slow rocking.

The blocking solution is discarded and 20ml fresh blocking solution containing the anti Rap1a antibody (Santa Cruz Biochemical SC1482) at 1:1000 (diluted in Western blocking buffer) and the anti Rab6 antibody (Santa Cruz Biochemical SC310) at 1:5000 (diluted in Western blocking buffer) are added. The membranes are incubated at room temperature for 1 hour with mild rocking. The blocking solution is then discarded and the membrane is washed 3 times with Western wash buffer for 15 minutes per wash. 20ml blocking solution containing 1:1000 (diluted in Western blocking buffer) each of two alkaline phosphatase conjugated antibodies (Alkaline phosphatase conjugated Anti-goat IgG and Alkaline phosphatase conjugated anti-rabbit IgG [Santa Cruz Biochemical]) is then added. The membrane is incubated for one hour and washed 3x as above.

About 2ml per gel of the Amersham ECF detection reagent is placed on an overhead transparency (ECF) and the PVDF membranes are placed face-down onto the detection reagent. This is incubated for one minute, then the membrane is placed onto a fresh transparency sheet.

The developed transparency sheet is scanned on a phosphorimager and the Rap1a Minimum Inhibitory Concentration is determined from the lowest concentration of compound that produces a detectable Rap1a Western signal. The Rap1a antibody used recognizes only unprenylated/unprocessed Rap1a, so that the precence of a detectable Rap1a Western signal is indicative of inhibition of Rap1a prenylation.

EXAMPLE 26

In vivo tumor growth inhibition assay (nude mouse)

In vivo efficacy as an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art. Examples

of such *in vivo* efficacy studies are described by N. E. Kohl et al. (*Nature Medicine*, 1:792-797 (1995)) and N. E. Kohl et al. (*Proc. Nat. Acad. Sci. U.S.A.*, 91:9141-9145 (1994)).

Rodent fibroblasts transformed with oncogenically mutated human Ha-*ras* or Ki-*ras* (10^6 cells/animal in 1 ml of DMEM salts) are injected subcutaneously into the left flank of 8-12 week old female nude mice (Harlan) on day 0. The mice in each oncogene group are randomly assigned to a vehicle, compound or combination treatment group. Animals are dosed subcutaneously starting on day 1 and daily for the duration of the experiment. Alternatively, the farnesyl-protein transferase inhibitor or combination composition may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.1 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 11-15 days after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is an inhibitor of farnesyl-protein transferase.

2. The composition according to Claim 1 wherein the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase.

3. The composition according to Claim 2 wherein the selective inhibitor of farnesyl-protein transferase is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 500 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

4. The composition according to Claim 2 wherein the selective inhibitor of farnesyl-protein transferase is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 100 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

5. The composition according to Claim 3 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

b) an IC_{50} (a measure of in vitro inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than

100-fold higher than the IC_{50} for the inhibition of the farnesylation of hDJ protein.

6. The composition according to Claim 3 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibition of K4B-Ras dependent activation of MAP kinases in cells at least 100-fold greater than the IC_{50} for inhibition of the farnesylation of the protein hDJ in cells.

7. The composition according to Claim 3 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

d) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells at least 1000 fold lower than the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

8. The composition according to Claim 3 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

b) an IC_{50} (a measure of in vitro inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than 100-fold higher than the IC_{50} for the inhibition of the farnesylation of hDJ protein in cells; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) against K4B-Ras dependent activation of MAP kinases in cells at least 100-fold greater than the IC_{50} for inhibition of the farnesylation of the protein hDJ in cells.

9. The composition according to Claim 1 which is characterized by:

a) inhibition of the cellular prenylation of greater than (>) about 50% of the newly synthesized K4B-Ras protein after incubation of assay cells with the compounds of the invention.

10. The composition according to Claim 1 which is characterized by:

b) inhibition of greater than about 50% the K4B-Ras dependent activation of MAP kinases in cells.

11. The composition according to Claim 1 which is characterized by:

c) inhibition of H-Ras dependent activation of MAP kinases in cells at least about 2 fold lower but less than about 20,000 fold lower than the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

12. The composition according to Claim 4 wherein the inhibitor of farnesyl-protein transferase is selected from:
5(S)-n-Butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

(S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl)-2-piperazinone

5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone

1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine

4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile (L-806,572)

4-{5-[4-Hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(5-Chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile

18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclononadecine-9-carbonitrile,

(±)-19,20-Dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile,

(±)-19,20-Dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile,

or the pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises

the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

31. The method according to Claim 21 wherein the inhibitor of farnesyl-protein transferase is selected from:
5(S)-n-Butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

(S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl)methyl)-2-piperazinone

5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone

1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone

1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine

4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile (L-806,572)

4-{5-[4-Hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(5-Chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-{3-[4-(2-Oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-ylmethyl}benzonitrile

4-[3-(2-Oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile

18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxaazacyclononadecine-9-carbonitrile,

(±)-19,20-Dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile,

(±)-19,20-Dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile,

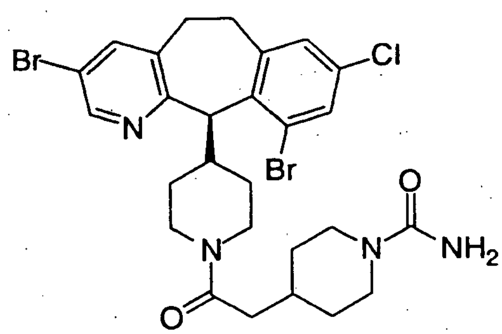
or the pharmaceutically acceptable salt thereof.

32. A method of inhibiting the growth of cancer cells which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition which comprises an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is:

(+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone

or the pharmaceutically acceptable salt thereof.

33. A method of inhibiting the growth of cancer cells which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition which comprises an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is:



or the pharmaceutically acceptable salt thereof.

34. The method according to Claim 20 wherein

the inhibitor of HMG-CoA reductase is selected from: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin, and the pharmaceutically acceptable lactone, open acid, salt and ester forms thereof.

35. The method according to Claim 20 wherein the amount of the inhibitor of HMG-CoA reductase is between about 0.1 mg per day and about 3000 mg per day.

36. The method according to Claim 35 wherein the amount of the inhibitor of HMG-CoA reductase is between about 0.3 mg per day and about 160 mg per day.

37. The method according to Claim 20 wherein the amount of the inhibitor of farnesyl-protein transferase is between about 10 mg per day and about 3000 mg per day.

38. The method according to Claim 37 wherein the amount of the inhibitor of farnesyl-protein transferase is between about 10 mg per day and about 1000 mg per day.

39. A method of inhibiting the growth of cancer cells which comprises administering to a mammal in need thereof an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is an inhibitor of farnesyl-protein transferase.

40. The method according to Claim 39 wherein the inhibitor of HMG-CoA reductase is administered prior to the administration of the inhibitor of farnesyl-protein transferase.

41. A method of inhibiting the growth of cancer cells in a mammal which comprises administering to said mammal an amount of a first compound which is an inhibitor of HMG-CoA

reductase and an amount of a second compound which is an inhibitor of farnesyl-protein transferase and applying to the mammal radiation therapy.

42. The method according to Claim 41 wherein the amount of an inhibitor of farnesyl-protein transferase and the radiation therapy are administered simultaneously.

43. The method according to Claim 41 wherein the amount of the inhibitor of HMG-CoA reductase and the amount of an inhibitor of farnesyl-protein transferase are administered first and the radiation therapy is administered after the the amount of an inhibitor of farnesyl-protein transferase has been administered.

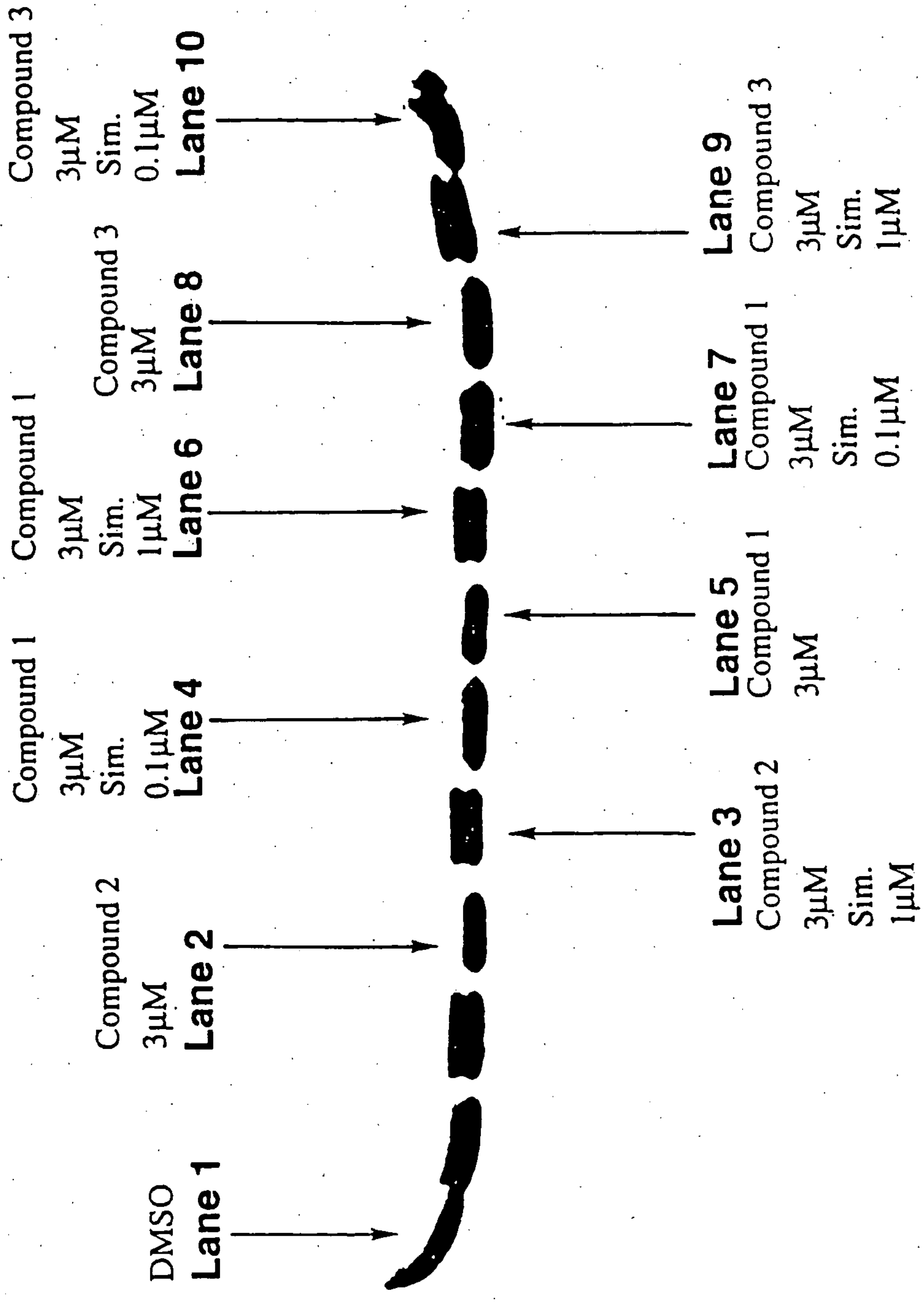

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FIGURE 1

SEQUENCE LISTING

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Heimbrook, David C.
Koblan, Kenneth S.
Oliff, Allen I.
Stirdivant, Steven M.

<120> A Method Of Treating Cancer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/21773

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505, 31/44, 31/415
US CL : 514/ 256, 290, 333, 341, 396, 460
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 256, 290, 333, 341, 396, 460

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, HCAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database HCAPLUS on STN, (Conumbus, OH, USA), ACCESSION No 127:331747, HEIMBROOK, D. 'Preparation of imidazole derivatives and imidazole-contg. peptide analogs and a method of treating cancer,' abstract, WO 97/36587, 09 October 1997.	1-43
X, P	WO 98/57633 A1 (PFIZER PRODUCTS INC.)23 December 1998, see abstract.	1-43

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 NOVEMBER 1999	04 FEB 2000

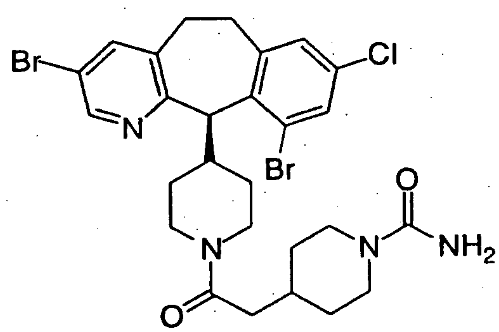
Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	REBECCA COOK
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is:

(+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone

or the pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition for achieving a therapeutic effect in a mammal in need thereof which comprises an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is:



or the pharmaceutically acceptable salt thereof.

15. The composition according to Claim 1 wherein the inhibitor of HMG-CoA reductase is selected from: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin, and the pharmaceutically acceptable lactone, open acid, salt and ester forms thereof.

16. The composition according to Claim 1 wherein the amount of the inhibitor of HMG-CoA reductase is between about 0.1 mg and about 3000 mg.

17. The composition according to Claim 16 wherein the amount of the inhibitor of HMG-CoA reductase is between about 0.3 and about 160 mg.

18. The composition according to Claim 1 wherein the amount of the inhibitor of farnesyl-protein transferase is between about 10 mg and about 3000 mg.

19. The composition according to Claim 18 wherein the amount of the inhibitor of farnesyl-protein transferase is between about 10 mg and about 1000 mg.

20. A method of inhibiting the growth of cancer cells which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition which comprises an amount of a first compound which is an inhibitor of HMG-CoA reductase and an amount of a second compound which is an inhibitor of farnesyl-protein transferase.

21. The method according to Claim 20 wherein the inhibitor of farnesyl-protein transferase is a selective inhibitor of farnesyl-protein transferase.

22. The method according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 500 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^{F}$ motif by farnesyl-protein transferase.

23. The method according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is characterized by:

a) an IC_{50} (a measurement of *in vitro* inhibitory activity) of less than about 100 nM against transfer of a farnesyl residue to a protein or peptide substrate comprising a $CAAX^F$ motif by farnesyl-protein transferase.

24. The composition according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

b) an IC_{50} (a measure of in vitro inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than 100-fold higher than the IC_{50} for the inhibition of the farnesylation of hDJ protein.

25. The composition according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) for inhibition of K4B-Ras dependent activation of MAP kinases in cells at least 100-fold greater than the IC_{50} for inhibition of the farnesylation of the protein hDJ in cells.

26. The method according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

d) an IC_{50} (a measurement of *in vitro* inhibitory activity) against H-Ras dependent activation of MAP kinases in cells at least 1000 fold lower than the inhibitory activity (IC_{50}) against H-*ras*-CVLL (SEQ.ID.NO.: 1) dependent activation of MAP kinases in cells.

27. The method according to Claim 21 wherein the selective inhibitor of farnesyl-protein transferase is further characterized by:

b) an IC_{50} (a measure of in vitro inhibitory activity) for inhibition of the prenylation of newly synthesized K-Ras protein more than 100-fold higher than the IC_{50} for the inhibition of the farnesylation of hDJ protein in cells; and

c) an IC_{50} (a measurement of *in vitro* inhibitory activity) against K4B-Ras dependent activation of MAP kinases in cells at least 100-fold greater than the IC_{50} for inhibition of the farnesylation of the protein hDJ in cells.

28. The method according to Claim 21 wherein the composition is characterized by:

a) inhibition of the cellular prenylation of greater than (>) about 50% of the newly synthesized K4B-Ras protein after incubation of assay cells with the compounds of the invention.

29. The method according to Claim 21 wherein the composition is characterized by:

b) inhibition of greater than about 50% the K4B-Ras dependent activation of MAP kinases in cells.

30. The method according to Claim 21 wherein the composition is characterized by:

c) inhibition of H-Ras dependent activation of MAP kinases in cells at least about 2 fold lower but less than about 20,000 fold lower than